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Washington, D. C. June 1–3, 1960

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INTERNATIONAL CONFERENCE ON SARCOIDOSIS

Washington D. C. June 1–3, 1960

The Division of Medical Sciences
National Academy of Sciences–National Research Council

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FOREWORD

It has been eighty-five years since Jonathan Hutchinson in Great Britain first recognized the skin manifestations of sarcoidosis. Although Hutchinson was a surgeon, neurologist, and ophthalmologist, as well as a dermatologist, it remained for Boeck in Norway, Besnier in France, and Schaumann and Löfgren in Sweden to complete the description of what is now recognized as a generalized granulomatous disease with protean manifestations.

A synthesis of pathologic and clinical descriptions led (in 1948) to a definition of sarcoidosis by a subcommittee in the Division of Medical Sciences of the National Academy of Sciences—National Research Council (NAS–NRC). This was revised in 1956 and has since served as a unifying conceptual description. Also under the auspices of the Division, the first epidemiologic study of this disease was undertaken in the United States. This work was financed by the Veterans Administration, and technical assistance was provided by the United States Public Health Service. Thus, it was entirely natural and logical for this International Conference on Sarcoidosis to be planned by the present NAS–NRC Committee on Sarcoidosis[1] and to be financed jointly by the National Institutes of Health and the Veterans Administration.

Despite an increasing knowledge of the characteristics of this disease, its cause remains unknown. Indeed, there is still a question whether sarcoidosis represents a single disease or a syndrome in response to many inciting agents. Although this problem alone seemed to justify the need for an international conference, an additional question has been raised as to whether the disease is the same in different parts of the world. Further, the true incidence and prevalence of sarcoidosis have not been established, despite the fact that in recent years the literature has been veritably deluged with case reports. For these reasons an effort was made to obtain epidemiologic information, even though preliminary and incomplete, from different parts of the world.

Therefore, the Committee on Sarcoidosis recommended a multidisciplinary approach to these unsolved problems. Clinicians, pathologists, epidemiologists, and a scattering of other specialists were invited to reveal fully all current information concerning the disease and to delineate the gaps in knowledge. In this way it was hoped that research directed toward these questions might be stimulated in many parts of the world.

We trust that those who attended this three-day meeting, and those who will have the opportunity to read the published transactions, will be in a somewhat better position to apply newer techniques and to introduce and test new hypotheses which ultimately will lead to an understanding of the etiology and natural history and to an improvement in the therapy of this fascinating disease.

The close of this Conference did not end the responsibilities of the Committee or the task of the NAS–NRC staff. The Committee was enriched and strongly supported in its effort to publish these Proceedings by the yeoman services of M. Dean Nefzger, who stepped in to assist us in organizing and editing the manuscripts which are included herein. He also coordinated all of the complex administrative affairs which led to publication. We are also indebted to Mrs. Myrtis E. Hillman, who served us all as hostess to the Conference and editorial assistant for the Committee. Recognition and appreciation are warmly given for the services of Miss Virginia R. Dorman, Mrs. Viola F. Thornberg, and Miss Martha R. Mendenhall, who did much of the typing and handling of necessary details leading to organization of the Conference and publication of its transactions.

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CONTENTS

Foreword. Martin M. Cummings i
Participants in the Conference v
Opening of Conference. R. Keith Cannan 1

Diagnostic Criteria

Introduction. Esmond R. Long 2
The Definition of Sarcoidosis. Harriet L. Hardy 2
The Morbid Anatomy of Sarcoidosis. Erwin A. Uehlinger 6
Clinical Concept of Sarcoidosis. D. Geraint James 14
The Concept of Sarcoidosis. Sven Löfgren 17
Etiologic Concept of Sarcoidosis. Harold L. Israel 20
Discussion 21
Summary. Max Michael, Jr. 24

Research on Clinical Aspects of Sarcoidosis

Calcium Metabolism in Sarcoidosis. Norman H. Bell, John R. Gill, Jr., and Frederic C. Bartter 27
Studies of the Production, Volume, and Destruction of Erythrocytes in Patients with Sarcoidosis. Martin E. Liebling, Norman H. Bell, and James M. Stengle 32
Ocular Aspects of Sarcoidosis. Lorenz E. Zimmerman and A. Edward Maumenee 38
Experimental Sarcoid Reactions in Human Skin. Walter B. Shelley and Harry J. Hurley, Jr. 45
Sarcoidosis in Children. Edwin L. Kendig, Jr. 49
Experimental Treatment with Chloroquine. James G. Hirsch 52
Discussion 53
Summary. Horace W. Bernton 58

The Natural History of Sarcoidosis

Introduction. Andrew C. Douglas 60
Course and Prognosis of Sarcoidosis: Philadelphia. Maurice Sones and Harold L. Israel 60
Course and Prognosis of Sarcoidosis: London. D. Geraint James 66
Course and Prognosis of Sarcoidosis: Stockholm. Sven Löfgren and Sven Stavenow 71
Discussion 72
Summary. Edward Dunner 73

Research on Granulomatous Diseases

Introduction. Carl T. Nelson 76
The Production of Experimental Granulomatous Lesions Induced by Injections of Fatty Acids and Fractions of Tubercle Bacilli. J. Ungar and P. W. Muggleton 76
Pine Pollen Granuloma in Animals. Ralph A. Vogel and Agatha M. Thrash 81
The Biologic Significance of Experimentally Induced Allergic Granulomas. Frederick G. Germuth, Jr. 84
The Preparation and Standardization of Kveim Testing Antigen. Merrill W. Chase 86
Current Status of the Nickerson-Kveim Reaction. Louis E. Siltzbach 89
Tissue Culture Observations in Sarcoidosis. Anna-Lisa Obel, Holger Lundbeck, and Sven Löfgren 94
Discussion 94
Summary. David T. Smith 101

Analysis of Incidence and Mortality Data in the United States

Introduction. Thomas D. Dublin 103
Sarcoidosis in the United States Army, 1952 through 1956. Joseph W. Cooch 103
Sarcoidosis in the United States Navy. Benjamin F. Gundelfinger and Sidney A. Britten 109
Mortality from Sarcoidosis in the United States. Iwao M. Moriyama 116
Sarcoidosis in New York City. Hans Abeles, Arthur B. Robins, and Aaron D. Chaves 120

Discussion ... 120
Summary. Philip E. Sartwell ... 122

Geographic Epidemiology of Sarcoidosis

Introduction. Martin M. Cummings ... 124
Geographic Epidemiology of Sarcoidosis in Florida. C. F. McCuiston, Max Michael, Jr., and Paul C. Hudgins ... 124
Clay Eating and Sarcoidosis. A Controlled Study in the State of Georgia. G. W. Comstock, H. Keltz, and D. J. Sencer ... 130
Geographic Epidemiology of Sarcoidosis in Denmark: 1954–1957. Ole Horwitz ... 135
Sarcoidosis in Scotland. Andrew C. Douglas ... 143
Epidemiology of Sarcoidosis in Japan. Preliminary Report. Keizo Nobechi ... 148
Epidemiology of Sarcoidosis in Switzerland. Erwin A. Uehlinger ... 153
Epidemiology of Sarcoidosis in Uruguay and Other Countries of Latin America. Pablo Purriel and Eduardo Navarrete ... 155
Sarcoidosis in South Africa. B. Van Lingen ... 162
Epidemiology of Sarcoidosis in the United States. Edward Dunner and John H. Williams, Jr. ... 163
Discussion ... 166
Summary. John S. Chapman ... 169

Plenary Session

Introduction. Robert J. Anderson ... 171
Report of the Medical Group. Harold L. Israel ... 171
Report of the Laboratory Group. David T. Smith ... 174
Report of the Epidemiology Group. Philip E. Sartwell ... 175
Discussion ... 175
Summary of Conference. Esmond R. Long ... 180

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OPENING OF CONFERENCE

R. KEITH CANNAN

This Conference meets under the aegis of the Division of Medical Sciences of the National Research Council. As Chairman of the Division, it is my privilege to invite you into formal session. It is my pleasure, also, to extend to all of you the greetings of the National Academy of Sciences and the National Research Council. Particularly, I would like to welcome our guests from overseas who have come a long way to share in our deliberations. We are honored by their presence and by the opportunity to share our experiences with them.

The subject of sarcoidosis is not just a passing whim of the Division of Medical Sciences. We have had a somewhat extended interest in the subject. It goes back to the end of World War II, when we were doing what we could to support the determination of the Veterans Administration to explore the unique potentialities for research of the veteran population and to organize the military and veteran medical records for the study of the natural history of appropriate diseases.

It was shortly after World War II that the suggestion was made that it would be appropriate for the Veterans Administration to conduct a follow-up study on those members of the military forces who carried the diagnosis of sarcoidosis. This led to our first National Sarcoidosis Conference in 1948. As was fitting, first things were put first at the Conference and agreement was sought on definitions and criteria of diagnosis.

Following the 1948 Conference, there was a period of sustained interest by the Veterans Administration, stimulated, I suspect, by the evangelism of Martin M. Cummings, and directed increasingly toward an epidemiologic approach.

By 1956, it seemed appropriate to call a second national conference. From this emerged the suggestion that the time was now ripe to confer on a wider level in the hope of reaching international agreement on basic matters and perhaps of developing an international approach to the investigation and the elucidation of the etiology of the disease.

This brings us to today, when we hold our first International Conference on Sarcoidosis under the aegis of the National Research Council. We are here not merely because of the sustained interest of the Division or even of the continuing and generous support of the Veterans Administration. In order that we might have the international representation that we sought and the means to publish the proceedings of this Conference, we turned to the National Institutes of Health and from them received a generous grant which, together with funds provided by the Veterans Administration, sustains this Conference. We are grateful for this interest, and we are most happy to acknowledge it.

Our task, then, is to sit down and talk to each other, but I hope it is not merely to talk and then complacently to go home. I think our purposes should be to seek agreement on the fundamental issues of definition, criteria, and so on, in order that we may move on from there and begin to lay plans for international exchange of ideas and programming. There is a feeling in the air that a coherent international effort at this time, particularly in respect to the epidemiology of sarcoidosis, could make a significant contribution to understanding. May your conference be rewarding both in scientific communication and in good fellowship.

DIAGNOSTIC CRITERIA

ESMOND R. LONG, *Moderator*

INTRODUCTION

DR. LONG: Dr. Cannan has outlined the history of the conferences that have been held under the sponsorship of our National Research Council on the subject of sarcoidosis. He stressed what cannot be stressed too much, the fact that now, more than ever, we are emphasizing the international aspects of cooperation.

We learned some time ago that it is important to bring into the picture the place of sarcoidosis as a disease in different countries. It is not always the same, as you know, and we may find some clues in the perplexing problems of etiology and prognosis from learning the experiences of those who come from other lands.

Dr. Cannan also made what seemed to me to be a very significant point, namely, the importance of sustained interest in each others' work after we leave the Conference. We hope that you who come to us from abroad will bear in mind our trust that we can work together as a group and share experiences.

I have always been intrigued by the word "moderator." I have taken part in a number of conferences that do require someone to exercise the virtue of moderation. Those of you who have participated in conferences on such subjects as BGG vaccination will recall that there can be even acrimony among those present in support of their own particular points of view. I never knew that any enemies were made, however, over the subject of sarcoidosis. There is a fairly wide divergence in views on the etiology of the disease, but there seems to be a good deal of harmony, in behavior at least, in our approach to the problem.

The keynote of any such conference as this should be informality. Everyone should participate. We are all here together as friends, and should be able to discuss matters quite freely. I believe the record of this Conference will be very valuable and that we will all read it with great interest when we come to review the work in which we are engaged this week.

As Dr. Cannan pointed out, in the course of our previous, more local conferences we have been concerned very much with the definition of the disease. I think most diseases are somewhat easier to define than sarcoidosis. It is essential that we continue to improve our definition of this disease as we go on.

THE DEFINITION OF SARCOIDOSIS[1]

HARRIET L. HARDY

It may be that my contribution under the title, "The Definition of Sarcoidosis," should be the last paper of the Conference rather than the first. I have had a kind of "Alice in Wonderland" period wandering through the literature and assembling my own ideas of what is this disease that I am to define. Is it possible to define a disease which lacks an agreed-on etiology? If it is possible to define sarcoidosis, is it wise? To insist on definition demands that limits be set. If definition is achieved, the study of sarcoidosis might be restricted by rules which unwittingly would exclude the development of data needed to achieve understanding of the pathogenesis of this interesting disease. The word "description" is a better working word than "definition." It may be helpful to future students of sarcoidosis to mention the year when formal description is offered to emphasize the fact that knowledge of the disease is incomplete and hopefully will develop.

It has been valuable and refreshing to me to go to the literature. I began with a look at the illustration of the case of curious skin lesions seen by Jonathan Hutchinson in 1869 and published in 1875 in his impressive book, *Illustrations of Clinical Surgery Consisting of Plates, Photographs, Wood Cuts, Diagrams, etc. Il-*

[1] From the Massachusetts General Hospital, Boston 14, Massachusetts.

lustrating Surgical Diseases, Symptoms and Accidents (*1*). I glanced next at Caesar Boeck's 1899 picture of a man with what he called multiple benign sarcoid of the skin (2), well known, of course, to you as the most often used reference of the disease we are discussing. Since the time of these observers, the eponyms are legion, as are the discussions of the clinical facets of the lesion associated with so-called sarcoidosis. Twenty-six years ago a symposium was held in Strasbourg on the subject of sarcoidosis but, since this was a meeting of the Réunion Dermatologique (3), skin manifestations were the chief concern.

I recite these historic facts not because I think they are new to you, but to introduce the subject of nomenclature. Undoubtedly, usage will preclude changing nomenclature, but a conference such as this one can consider such a possibility. Sarcoid was suggested because the microscopic picture of the lesions he described brought to Boeck's mind sarcoma—tumor of the flesh (4). This term is certainly neither definitive nor descriptive of our present knowledge of this disease. In using the word "sarcoidosis," a clinical entity is implied which frequently presents no lesions of the flesh. The steadily increasing use of the phrase "sarcoid-like lesion," at least in the United States, compounds the inaccurate reference, since the term may be used for foreign body reactions or may refer to many unexpected lesions found at autopsy appearing to be, as Schaumann (5) put it, "benign lymphogranulomata." Some of the eponyms associated with the disease, sarcoidosis, which we are discussing are listed below.

Eponyms

Hutchinson's "Papillary psoriasis," "Mortimer's malady"		1869
Besnier	Lupus pernio	1889
Boeck	Multiple benign sarcoid	1899
Boeck	Benign miliary lupoid	1905
Heerfordt	Uveoparotid fever	1909
Jungling	Osteitis tuberculosa multiplex cystica	1911
Schaumann	Benign lymphogranuloma	1917

What is wanted is a title which will communicate to all a description of a disease of unknown cause, with a variety of syndromes held together by a history of common clinical and pathologic observations.

Many writers refer to Hodgkin's disease when writing of sarcoidosis because of similarities in the past history and present state of knowledge of this entity. The eponymn, Hodgkin's disease, now universally used, carries an understanding of the clinical and pathologic character of a disease without presently known etiology. I suggest to this Conference that understanding may be increased by similar nomenclature for sarcoidosis. "Hutchinson's disease" would be the correct name if earliest record is the criterion (6). On the other hand, with usage as perhaps a better standard, sarcoidosis should continue to be called Boeck's disease. The pathologists have a wealth of terms for describing what they see in this disease: epithelioid bodies, granulomas, and so on, and have no need that I can discover for continuing the term "sarcoid." Further, it is in error for clinicians to refer to a disease as granulomatous without benefit of biopsy or autopsy. The use of the word "disease" and an eponym may lead to greater clarity in considering the diagnostic problem associated with a wide variety of clinical syndromes without etiology, as, for example, that commonly seen with miliary chest roentgenographic changes without symptoms.

I beg off then from a definition, but agree to describe a disease. In addition, in the interest of more accurate nomenclature, I urge substituting the title "Hutchinson's" or "Boeck's" disease for the present title "sarcoidosis."

Without asking him, I have assumed that the chairman who assigned me my topic had in mind that I might speak briefly of the accumulating knowledge of certain man-made diseases, the occupational or industrial diseases. Such knowledge, since it can be correlated with etiology, may be helpful in describing Boeck's disease. For, if the occupational disease mimics faithfully the disease of unknown cause that we are studying at this meeting, it may be that knowledge of the mechanism of production of the occupational illness may lead to understanding of the pathogenesis and etiology of Boeck's disease.

Dr. David Freiman (7), at the 1958 Symposium on Beryllium Diseases in Cambridge, cited a case of "farmer's lung" in discussing the difficulty of depending on pathologic findings for the diagnosis of beryllium disease. Using a slide of lung tissue taken at biopsy, Dr. Freiman pointed out the nonspecificity of the microscopic picture of many granulomatous diseases. While the detail of pathogenesis of farmer's lung is not worked out, all those reporting this disease agree that it is caused by the inhalation of mold dust arising

usually from various fodder crops stored while wet and used later (8).

Dr. Kovnat, of Miami, Florida, showed me the case report of a young woman assisting in a dental laboratory where she was exposed to very high levels of finely divided aluminum dust. The woman had no complaints, but had a dramatic-appearing chest roentgenogram showing widespread parenchymal densities. A lung biopsy showed a benign granulomatous process, perhaps a foreign-body reaction that might be called, in current terminology, a man-made sarcoid.

In my experience, I have had occasion to study several machinists who, following exposure to dusts of a number of elements, developed a picture first considered tuberculosis, then Boeck's disease and, finally, perhaps chemical granuloma. The assay of the tissue biopsied from these cases showed the presence of tin in abnormal amounts. Epidemiologic evidence will be required to make certain that the exposure at work is responsible for a reaction of this type.

These cases are examples of granulomatous disease localized in the lung. Similar reports can be found in the literature of the effect of certain silicates in the lung. Further, certain compounds of zirconium implanted in the skin cause localized noncaseating granulomas in some persons.

In sharp contrast is beryllium disease, which is a chemical intoxication with constitutional effects and capable of involving a number of organs.

For example, the lung biopsy of a 32-year-old male who worked very close to the place where rejected fluorescent lamps were broken, no precautions being taken against dust, showed beryllium in the tissue and noncaseating granulomas. The clinical course of the disease was characteristic of beryllium disease. The patient claimed to have been short of breath since 1951, with periods of worsening of the symptom, especially at times of even mild respiratory infection. At some time in his illness he had shown splenomegaly, hyperglobulinemia, hypercalciuria, and hilar adenopathy, as well as miliary parenchymal pulmonary nodulation.

A 22-year-old man was referred for study with a tentative diagnosis of chronic beryllium poisoning. It was thought that chemical intoxication was the result of the fact that the patient lived not far from an industrial plant where certain workers were known to have acquired the disease. Alveolar capillary block found on lung function study and an increase in serum protein, with a relative increase in the globulin fraction reported in this case, were identical with the changes in these indices found in the previous case of beryllium disease. However, study of a lung biopsy showed no beryllium in the lung tissue, and a diagnosis of Boeck's disease was made.

These 2 cases illustrate the problem of differential diagnosis between beryllium disease and sarcoidosis.

As knowledge of beryllium poisoning increases, the striking similarity to Boeck's disease is emphasized. On the other hand, there are definite differences as shown below.

Features of Sarcoidosis Absent from Beryllium Disease (1960)

Hilar adenopathy alone
Eye involvement
Uveoparotid fever
Cystic bone changes
Susceptibility to tuberculosis
Response to therapy
Skin reactivity (not well studied)

In studying the literature, I was struck with the marked differences between series of cases of Boeck's disease reported either at different times or from different geographic areas. For example, within the Longcope and Freiman (1952) report of 160 cases (9), the writers point out such differences between the cases seen in Baltimore and those in Boston. Certain differences were assigned to the interest of specialists such as dermatologists and ophthalmologists. In addition, such striking facts as greater evidence of effect on the heart and the number of cases of uveoparotid fever in the Baltimore group contrasted with renal impairment and enlargement of the spleen in the Boston group. If such differences occur in statistically significant numbers in world-wide studies, it may be that various syndromes now named Boeck's disease are no more closely related to each other than they are to the occupational disease, beryllium poisoning.

What then is a working description of Boeck's disease or, as it is called in the title of this Conference, sarcoidosis? As a result of my reading and experience, I find the conclusions of Longcope and Freiman (9) the most useful, and I am in debt to them for these concluding sentences:

Boeck's disease is common, frequently undiagnosed or misdiagnosed. Of presently unrecognized cause, it is a disease of long duration with

remissions which may be mistaken for cures, and exacerbations that may reflect progression of the disease or involvement of another organ. The granulomata or epithelioid tubercles and accompanying diffuse cellular reaction may do damage by replacement or mechanical injury. These pathologic lesions may heal slowly, or they may spread and cause death or organ destruction. Boeck's disease is of such protean character and mysterious behavior as to offer challenge to clinical observers and investigators from many fields.

This, I believe, is the best description presently at hand. I suggest we are not now ready for a definition.

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THE MORBID ANATOMY OF SARCOIDOSIS[1]

ERWIN A. UEHLINGER

Introduction

Anatomically, sarcoidosis is characterized by a predominant localization in the skin, lymph nodes, and lungs. Chronicity and tuberculin anergy are the decisive features of the disease. Therefore, caution must be exercised in making the diagnosis of sarcoidosis from the histology of lymph node material. It can be given presumptively; never with final certainty.

Morbid Anatomy of the Elementary Process

The basic process is the sarcoid granuloma (figure 1), a nodule of millet-seed size composed of epithelioid cells which, in time, become completely hyalinized. The granuloma can be differentiated from a tubercle in the following respects: (*a*) The epithelioid cells are arranged loosely, not compactly, in a radial fashion; (*b*) the granuloma demonstrates neither central caseation nor the formation of a peripheral wall of lymphocytes.

Upon careful screening of lymph nodes with sarcoid tissue, one sees, incidentally, regressive processes in the center of the granuloma, processes characterized by an eosinophilic degeneration of the cytoplasm and by a concentric shrinkage of the nuclei. This necrobiotic process can clearly be differentiated from tuberculous caseation with nuclear disintegration and cytoplasmic coagulation. Although Langhans' giant cells are often absent, their presence does not preclude sarcoidosis. Frequently, and especially in the giant cells (figure 2), concentrically layered calcific masses, rod-shaped elastic fibers encrusted with calcium and iron, the so-called Schaumann bodies, and star-shaped protein crystal rosettes—the asteroid bodies—may be seen (figure 3).

The final transformation of the granuloma takes place in a completely regulated manner. It begins with the formation of discrete hyaline clumps at the extreme periphery of the granuloma (figure 4). These clumps then fuse to girdle the nodule. Thereafter, hyaline masses are precipitated in the center of the granuloma. Simultaneously, collagen or argentophil fibrils, which are spun out into curious spirals and which interlace to form a wide-meshed, basket-like surface network, are differentiated between the epithelioid cells. Then the epithelioid cells shrink, the argentophil fibrils are encrusted with hyaline collagen, and the entire complex becomes, as it were, welded into a spherical pentagon-like mass (figure 5).

The anatomic constancy of the histologic findings in sarcoidosis corresponds to its clinical stability and chronicity. Biopsies taken at eleven-year intervals from the same patient can show exactly the same picture—in short, reactive conservatism.

The entire picture is one of monotonous unity, a paragon, so to speak, of tranquility, composure, and stability. This peacefulness and torpidity, then, is the decisive feature which distinguishes the sarcoid granuloma from the tubercle, in which the entire sequence of events, granuloma formation, caseation, and fibrosis can be easily followed.

Hyaline transformation, arranged in a sector-like fashion, can be observed in the nodules. Within these hyalinized islands, the giant cells remain intact for a strikingly long period. At first, only certain sectors on the perihilar lymph node undergo hyaline transformation, during which time the remaining part of the node is still densely filled with giant cell granulomas.

As a rule, the lymph nodes are completely permeated with densely and diffusely arranged granulomas of the same size, form, and structure.

Over-all Picture of the Morbid Anatomy

Fundamentally, two developmental phases, localization and generalization, can be distinguished in sarcoidosis. The phase of localization involves the tracheobronchial lymph nodes. Two types of the generalization phase can be differentiated in the lungs, namely, lymphogenous, possibly a retrograde dissemination originating from the hilar lymph nodes (figure 6), and hematogenous. The hematogenous type of the generalization phase is similar to the hematogenous dissemination of tuberculosis.

In both tuberculosis and sarcoidosis, the metastatic field includes both the lungs and extrapulmonary organs. Whereas the extrapulmonary organs favored by a tuberculous dissemination are the meninges, the skeletal and urogenital systems, and the joint capsules, a sarcoidal spread shows preference for the skin, reticuloendothelial system, salivary and tear glands, chorioidea, and both skeletal and heart muscles. The meninges, perivascular lymph vessels, kidneys, and thyroid are less often involved. It is to be emphasized that sarcoidosis

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never metastasizes in tendon sheaths, bursas, or joints, or in the adrenals or genital organs.

The importance of this unique metastatic target area cannot be overemphasized in the subclassification of the generalization phase of sarcoidosis in which the following forms can be differentiated:

(*a*) Dermatosarcoidosis, such as lupus pernio
(*b*) Reticuloendothelial sarcoidosis
(*c*) Sarcoidosis of the liver, spleen, and bone marrow
(*d*) Sarcoidosis of the salivary and tear glands (Heerfordt syndrome)
(*e*) Renal sarcoidosis
(*f*) Skeletal sarcoidosis
(*g*) Meningocerebral sarcoidosis
(*h*) Gastrointestinal sarcoidosis.

These forms of the generalization phase can combine in different ways, and the dissemination can occur simultaneously or successively.

Roentgenography: Sarcoidosis of the hilar lymph nodes of the lung as demonstrated by roentgenography is characterized in its localization phase by the bilateral symmetry and the tumor-like, polycyclic enlargement of the hilar lymph nodes. The generalization phase is marked by the increased density in the middle and lower regions of the lungs, by the lack of pleural adhesions in the phrenicocostal sinus and, in the later phase, by a cor pulmonale.

In relation to metastasis in the lung there are essentially three types to be differentiated through roentgenography: the miliary and nodular spotting, both with a transition into a systematic fibrosis; or an exaggeration of the reticulonodular lung pattern.

Histologic study: It may be seen histologically that the spotting results from a beadlike perivascular, peribronchial, and interstitial creeping of miliary granulomas in different phases of hyaline transformation. Within these areas, elastic remnants of the alveolar framework and vascular membranes, as well as giant and dust cells, can still be seen. With increasing hyalinization and dehydration of the hyaline, a reshaping of the shadows occurs. The scar tissue is divided into strands, with a resulting traction emphysema between strands. Of special significance is the severe scar-tissue traction toward the hilus which induces a compensatory emphysema in the lung periphery (figure 7). This intense scarification of the hilar area unquestionably deforms the bronchi and results in a macrobronchial stenosis. Therefore, in addition to a traction emphysema, an obstructive emphysema is added to the picture.

The obstructive lung emphysema arising from the hilar bronchial compression and deformation must be differentiated from the obstructive emphysema resulting from sarcoidosis of the bronchial mucosa. This latter form has been especially described by Turiaf. The histologic picture is characterized by numerous noncaseous subepithelial granulomas, particularly in the mucosa of the smaller bronchi and bronchioles, whereby a bronchiolostenosis occurs at the point where the lumen is narrowest, that is to say, where the respiratory bronchioli merge into the alveoli.

The significance of this state of affairs lies in the fact that, despite the resulting ventilation obstruction, the cause cannot be elucidated by roentgenography. The bronchiolo-sarcoidosis is, therefore, very difficult to diagnose for the following reasons: (*a*) The nodule formation is limited to the bronchial mucosa; (*b*) the tracheobronchial lymph nodes are usually scarcely involved and, therefore, not enlarged; (*c*) extrathoracic organs are generally not involved.

The diffuse colonizing of the bronchial mucosa with epithelioid cell nodules is one of the basic phenomena of sarcoidosis, and never occurs in this form in tuberculosis.

It is to be noted that tuberculosis of the bronchial mucosa never extends for a distance of more than 1 cm. from its point of contact with a cavity or a ruptured lymph node. This fact, then, can also be invoked in differential diagnostic problems. The diagnosis can only be made by a bronchial biopsy (figure 10).

Extrapulmonary sarcoidosis: Sarcoidosis of the skeleton, myocardium, striated musculature, and central nervous system deserves special mention among the extrapulmonary forms of the disease. Skeletal sarcoidosis, although a frequent finding, seldom manifests itself clinically, and then does so exclusively by lesions in the phalanges, whereby a remodeling of the spongiosa results in a roentgenographically demonstrable cyst formation. Nodule formation consists of plastic epithelioid giant-cell granulomas, often clustered in groups and sitting directly on the bone trabeculae. These nodules are in no way responsible for the often present hypercalcemia.

Diagnostic procedures: The diagnostic procedures available for the detection of sarcoidosis

include the following procedures for its morphologic determination by the pathologist:

(*a*) Skin biopsy (figure 8).
(*b*) Biopsy material obtained from peripheral lymph nodes (figure 1).
(*c*) Biopsy material obtained from *Daniel* lymph node (figure 9), which is known as the prescalene lymph node. The biopsy consists of the removal of the entire scalene fat pad, with occasional inclusion of elements of the jugular chain.
(*d*) Bronchial biopsy (figure 10).
(*e*) Liver puncture biopsy (figure 11).
(*f*) Bone marrow puncture biopsy (figure 12).
(*g*) Skeletal muscle biopsy (figures 13 and 14).

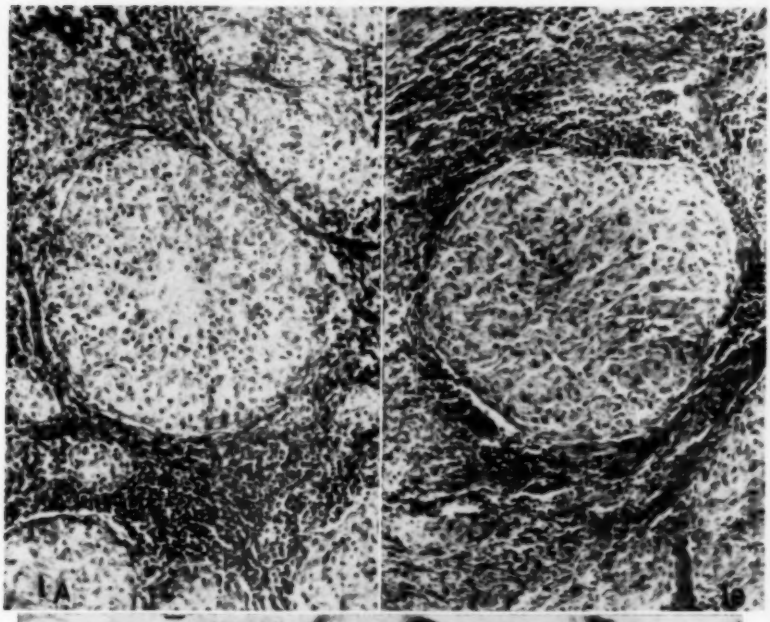
Daniel's biopsy is regularly positive in the event of lung sarcoidosis and bilateral hilar lymphadenopathy (figure 9).

The *bronchial biopsy* is especially important for the detection of sarcoidosis of the bronchial mucosa with bronchial stenosis and obstructive emphysema of the lungs (figure 10).

Liver puncture biopsy: In numerous cases of sarcoidosis, the liver biopsy is positive. However, it must be pointed out that miliary tuberculosis and sarcoidosis can scarcely be differentiated from each other in biopsy material. The diagnosis must be made, therefore, from the over-all picture, and never from a biopsy alone (figure 11).

The *bone marrow puncture biopsy* is only exceptionally positive. A negative result cannot be evaluated against sarcoidosis. Only a positive finding is decisive. Positive bone marrow punctures with sarcoid nodules are most likely to be found by those generalized forms which involve the spleen especially (figure 12).

Of paramount significance diagnostically are lesions in the *skeletal musculature.* Muscle granulomas occur in about 20 per cent of the cases. Despite granulomatous formation, especially in breast, shoulder, arm, and calf musculature, it is not possible, clinically, to speak of a muscular form of the disease. As a rule, the muscle foci are symptomless; only exceptionally skin or muscle nodes can be palpated. Muscular pain, weakness, or atrophy are even more exceptional. A positive muscle biopsy is consistent with the diagnosis of generalized sarcoidosis (figures 13 and 14).



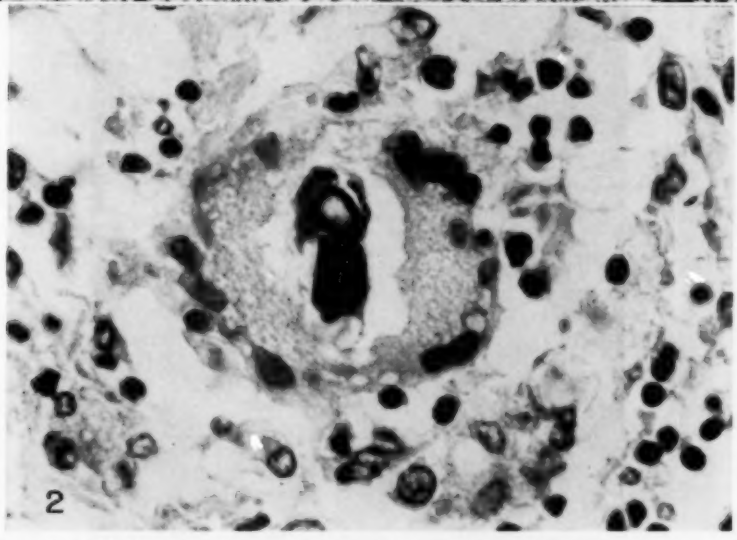


FIG. 1. Sarcoidosis. Granuloma of tuberculoid type. Lymph nodes. *A*. Biopsy, 1943. *B*. Biopsy, 1954, eleven years later. The man was twenty-six years old in 1943 (MB. 2720/43 and 1944/54). (Hematoxylin and eosin stain)

FIG. 2. Sarcoidosis. Foreign body giant cell with Schaumann body. Fifty-four-year-old woman (SN. 793/60). (Hematoxylin and eosin stain, × 780)

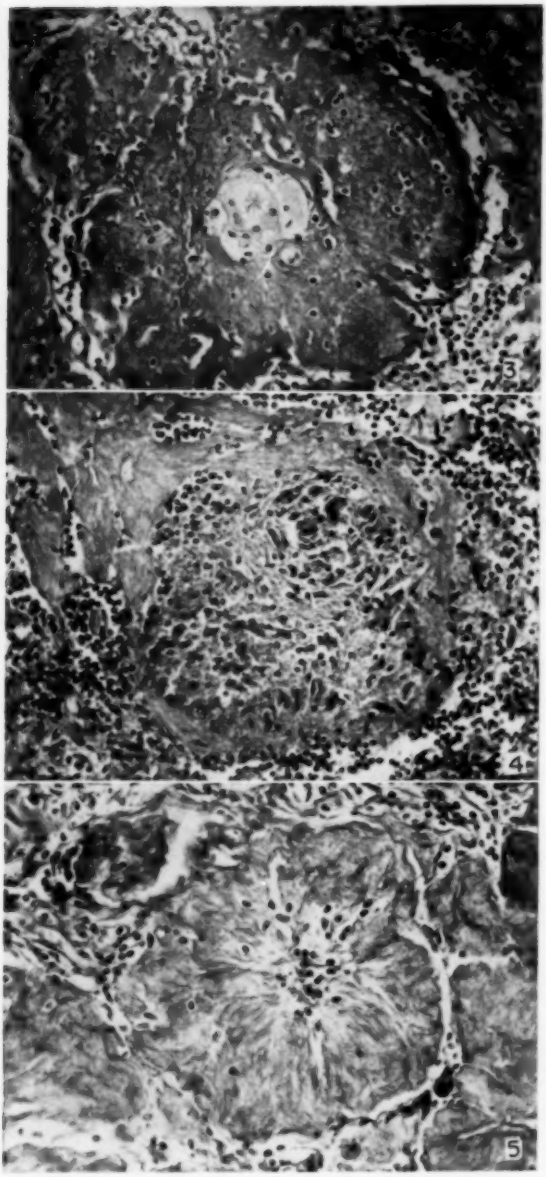


FIG. 3. Sarcoid granuloma in hyalinization. In center, a foreign body giant cell with inclusion of an asteroid body. Lymph node. Twenty-six-year-old woman (MB. 1094/58). (van Gieson stain, × 240)

FIG. 4. Sarcoid granuloma with peripheral hyalinization. Lymph node. Twenty-seven-year-old man (SN. 890/38). Hematoxylin and eosin stain, × 220)

FIG. 5. Sarcoid granuloma totally hyalinized. Lymph node. Twenty-six-year-old woman (MB. 1094/58). (van Gieson stain, × 300)

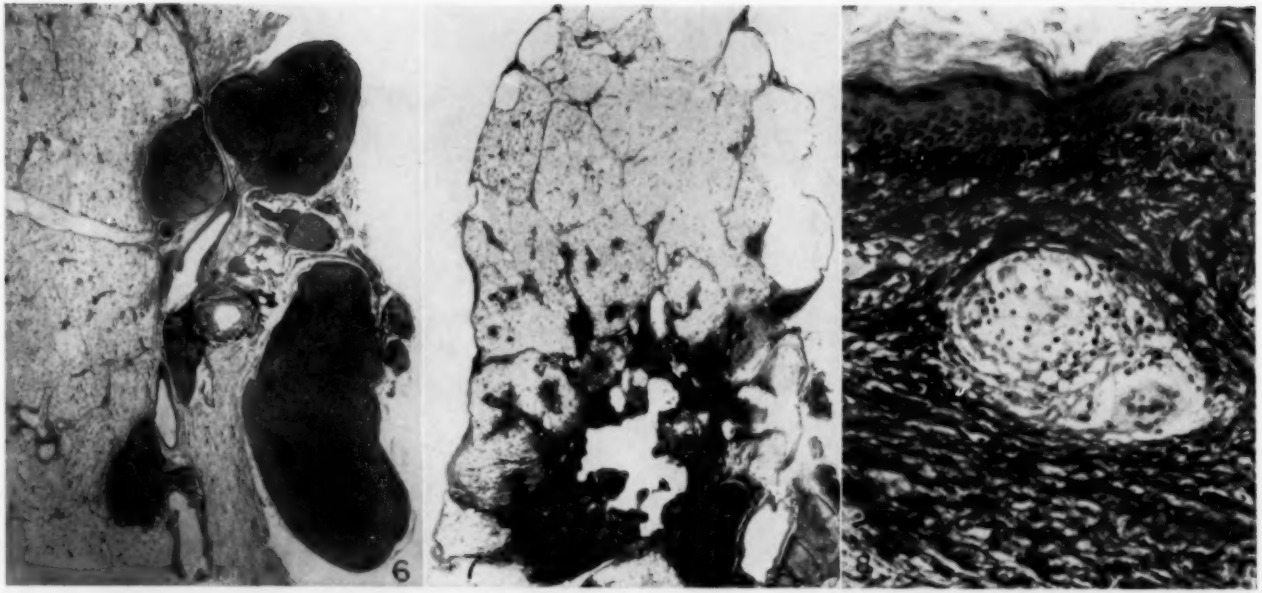


FIG. 6. Sarcoidosis. Bilateral hilar adenopathy. Fifty-four-year-old woman (SN. 793/60). (Hematoxylin and eosin stain)
FIG. 7. Sarcoidosis of lungs and hilar lymph nodes. Complete hyalinization of the hilar region. Compensatory bullous emphysema in the periphery of the lobe. Forty-year-old man (SN. 791/54). (van Gieson stain)
FIG. 8. Skin biopsy with sarcoid granuloma. Fifty-eight-year-old woman (SN. 1872/57). (van Gieson stain, × 200)

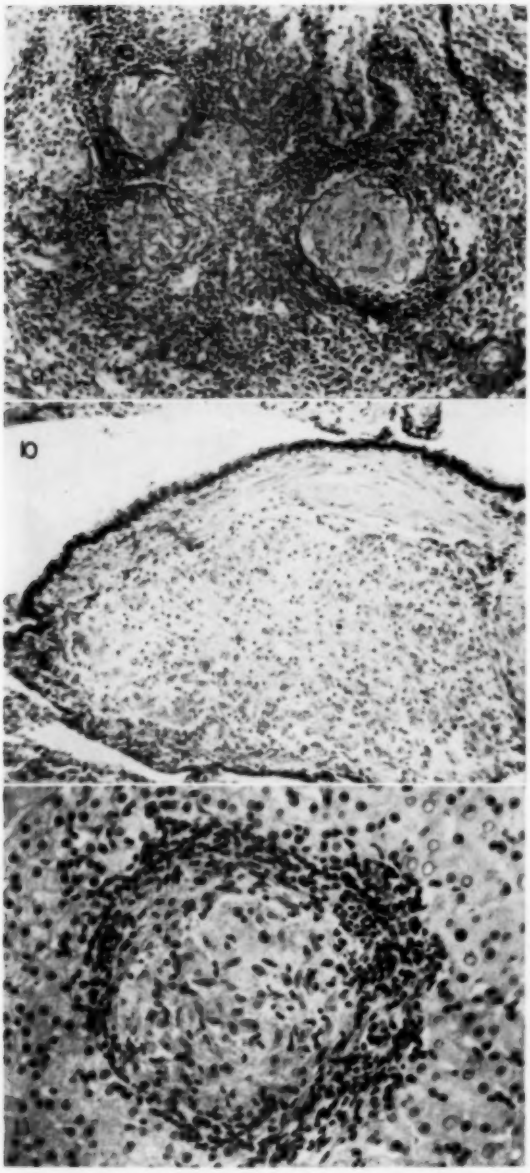


FIG. 9. Scalenus lymph node (Daniel's biopsy) with sarcoid granulomas of tuberculoid type. Forty-year-old woman (MB. 4836/57). (Hematoxylin and eosin stain, × 160)

FIG. 10. Bronchial biopsy with sarcoid granuloma. Fifty-six-year-old man (SN. 65/54 SG). (van Gieson stain, × 160)

FIG. 11. Sarcoid granuloma. Liver, puncture biopsy. Forty-three-year-old woman (MB. 13222/57). (Hematoxylin and eosin stain, × 250)

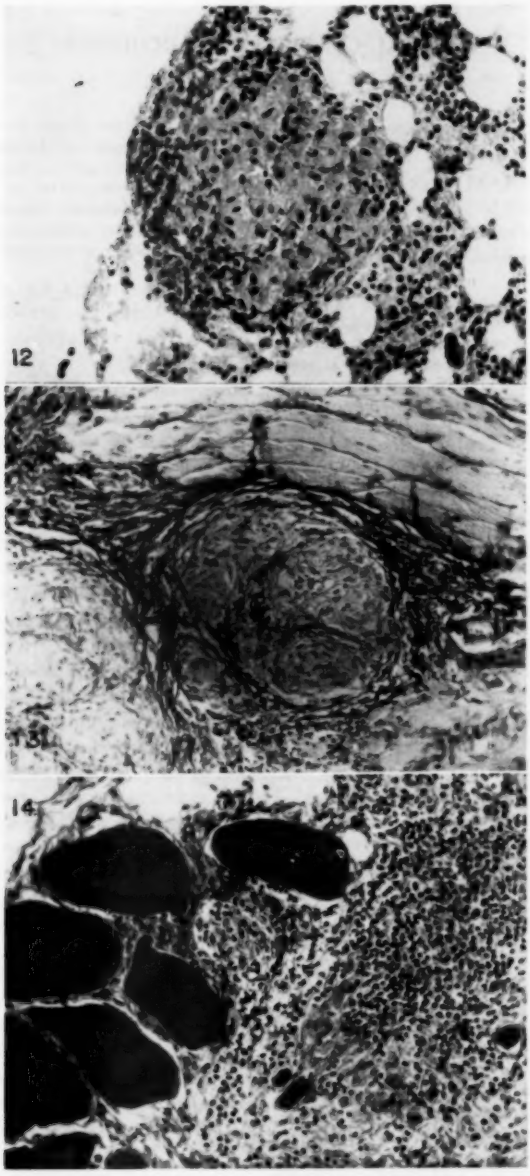


FIG. 12. Bone marrow with sarcoid granuloma. Puncture biopsy from sternum. Twenty-six-year-old man (MB. 2194/38). (Hematoxylin and eosin stain, × 260)

FIG. 13. Sarcoidosis of the striated muscles. Biopsy from the forearm. Twenty-nine-year-old man (MB. 13894/56). (Hematoxylin and eosin stain, × 160)

FIG. 14. Sarcoidosis of the striated muscles. Biopsy from the forearm. Sixty-five-year-old woman (MB. 5991/51). (Hematoxylin and eosin stain, × 180)

CLINICAL CONCEPT OF SARCOIDOSIS[1]

D. GERAINT JAMES

In our present state of ignorance concerning sarcoidosis, endeavors to define it are usually speculative, contentious, and unrewarding. In this communication, I prefer to project a factual concept based on an analysis of patients personally investigated in a sarcoidosis clinic at the Middlesex and Royal Northern Hospitals, London.

During a five-year period, 603 patients attended the clinic; they had been followed for various periods, but none for less than two years. It may be seen that patients are classified into six groups (table 1). The first two groups are composed of patients with a compatible clinical picture, and histologic confirmation of sarcoidosis was obtained by conventional means. The combination of clinical and histologic evidence defines them as universally acceptable examples of sarcoidosis as we recognize it today.

The third group exhibits the same clinical pattern, but histologic confirmation rests on the Kveim test. I accept these also as examples of sarcoidosis, although perhaps this may provide grounds for controversy.

The fourth group comprises patients with an acceptable clinical syndrome, but no histologic confirmation was obtained. Although these patients probably had sarcoidosis and were managed as such patients, they are excluded from analysis in this series because of the absence of histologic evidence.

The fifth group consists of patients in whom evidence of sarcoid tissue had been found in one or another system, but in whom there was no compatible clinical picture of the generalized disease. These are excluded from analysis, for they are examples of local sarcoid-tissue reactions and are quite unrelated to the generalized disorder—sarcoidosis. Local sarcoid-tissue reactions may be observed in lymph nodes draining carcinomas, in areas of Hodgkin's disease, as a response to infections and, commonly, in such areas as a chalazion of the eye. The lack of clinical evidence of sarcoidosis and a negative Kveim test are helpful in delineating this group. It is evident from world literature that these nonspecific local sarcoid-tissue reactions are confused with diffuse sarcoidosis, so beware of that special article which, for instance, may review the world literature of sarcoidosis of the tongue and add another example based on the finding of granulomatous tissue in the wall of an ulcer of the tongue.

I draw attention to the sixth and last group of other diseases unrelated to sarcoidosis but constituting a significant number of patients attending a sarcoidosis clinic. They had been referred because of superficial clinical or roentgenographic resemblances to sarcoidosis, so they must be regarded as representative of the day-to-day differential diagnosis of sarcoidosis. This group includes pulmonary tuberculosis, reticuloses, hepatic cirrhosis, and various skin and eye disorders.

My basic criteria for the diagnosis of sarcoidosis, certainly for investigative analysis, demand a compatible clinical picture and histologic evidence of sarcoid tissue, either from an involved tissue system or by means of the Kveim test (table 2). Thus, my material for presentation to this conference is based on 387 patients belonging to groups 1, 2, and 3 (table 1). They comprise 126 patients with erythema nodosum and 261 with other forms of the disease (tables 3 and 4). My analysis segregates erythema nodosum from other manifestations, for otherwise results would be as misleading and confusing as they would if, say, primary and adult tuberculosis were combined for purposes of analysis. The distinction will also lead, in due course, to my concept of subacute and chronic sarcoidosis. Erythema nodosum is the best example of acute transient sarcoidosis. It lasts only about three weeks and one can confidently predict that it will not recur if due to sarcoidosis. Bilateral hilar adenopathy, which so frequently accompanies it, is also practically always transient and can be expected to subside spontaneously within one year. This syndrome usually presents in young adult women of the third decade, an earlier age group than those with established skin and eye lesions (figure 15). From this original model of transient subacute sarcoidosis, let us examine the other manifestations of sarcoidosis to determine whether, by age at onset, course, and prognosis, they can also be categorized into subacute transient or chronic persistent varieties.

Here, then, is my concept of two types of sarcoidosis, differing in mode of onset, age incidence, course, prognosis, histology, and response to corticosteroid therapy (table 5). In making what appears to be a clear-cut distinction, I must not overstate my case, for clearly these are not two watertight compartments. We know full well that the age of thirty is but arbitrary, and that acute may progress to chronic iridocyclitis.

[1] From the Royal Northern Hospital, London, England.

TABLE 1

603 PATIENTS ATTENDING SARCOIDOSIS CLINIC

Group	Features	Number of Cases
1	Compatible clinical picture; Histologic confirmation; Kveim test positive	96
2	Compatible clinical picture; Histologic confirmation; Kveim test not done or negative	102
3	Compatible clinical picture; Kveim test positive	189
4	Compatible clinical picture; No histologic confirmation	36
5	Sarcoid histology; Kveim test negative	15
6	Other diseases	165
Total		603

TABLE 2

603 PATIENTS ATTENDING SARCOIDOSIS CLINIC

Compatible clinical picture	+	+	+	+	−	−
Histologic confirmation	+	+	−	−	+	−
Kveim test	+	−/ND*	+	−	−	−
	96	102	189	36	15	165

* −/ND: negative or not done

TABLE 3

MODES OF PRESENTATION OF SARCOIDOSIS IN 261 PATIENTS; ERYTHEMA NODOSUM EXCLUDED

	Number	Per Cent
Routine roentgenography	93	
Dyspnea	29	
Other respiratory disease	29	61
Malaise due to radiography	11	
Weight loss due to radiography	5	
Eye involvement	41	15
Skin lesions	19	7
Lymphadenopathy	18	
Polyarthralgia	15	
Parotitis	4	
Miscellaneous	10	

TABLE 4

SYSTEMS INVOLVED IN 261 PATIENTS WITH SARCOIDOSIS, EXCLUDING ERYTHEMA NODOSUM

	Number	Per Cent
Intrathoracic	219	84
Lymph nodes	100	38
Eyes	80	31
Skin	56	21
Spleen	41	15
Bone	17	7
Salivary glands	17	7
Nervous system	13	5
Lacrimal glands	4	—
Kidney	4	—
Muscle	3	—

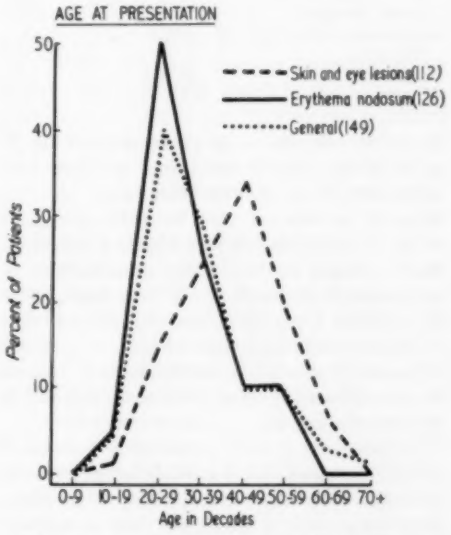


FIG. 15. Age of patients presenting with erythema nodosum, skin and eye lesions, and other (general) manifestations of sarcoidosis.

We may witness bilateral hilar lymphadenopathy progressing to a stage of diffuse pulmonary mottling or even to pulmonary fibrosis.

Nevertheless, as in the case of acute and chronic nephritis or hepatitis, the differences are sufficiently clear-cut to be of practical value. Transient subacute sarcoidosis exhibits a high incidence of spontaneous remission, whereas this is rarely observed in chronic sarcoidosis. Successes which have been claimed in the past for various cures with drugs or radiotherapy are presumably

TABLE 5

A Comparison of Subacute and Chronic Sarcoidosis

	Subacute, Transient	Chronic, Persistent
Age	Less than 30	30 and older
Onset	Abrupt	Insidious
Skin	Erythema nodosum; maculopapular rash; vesicular eruptions	Plaques; keloids; lupus pernio
Eyes	Conjunctivitis; acute uveitis	Keratoconjunctivitis sicca; chronic uveitis; cataract; glaucoma
Lungs	Hilar adenopathy	Pulmonary mottling
Bone cysts	Absent	Present
Bell's palsy Parotitis Lymphadenopathy	Yes	Rarely persist
Histology	Epithelioid and giant cells	Healing fibrosis
Calcium metabolism	Hypercalcemia; hypercalciuria	Nephrocalcinosis
Kveim test	Positive	May be negative
Spontaneous remission	Frequent	Rare
Steroid therapy	Abortive effect	Symptomatic relief
Recurrence after steroid therapy	Rare	Frequent
Prognosis	Good	Poor

due to this coincidental spontaneous remission. In planning any clinical trials, such as those with corticosteroids or hydroxychloroquine, the two forms of the disease must be distinguished, or results of the trials will be misleading. Similarly, those engaged in metabolic, immunologic, or epidemiologic studies should be clear-minded as to the different types when analyzing their results.

Finally, any discussion of the course and prognosis of sarcoidosis must take into account the two different types of the disease. This will be the theme of my later communication.

In summary: I have presented a concept of sarcoidosis based on an analysis of 387 patients personally investigated and followed for more than two years in a sarcoidosis clinic in London. The basic criteria for their inclusion in this series were twofold, namely, a compatible clinical picture and histologic evidence of sarcoid tissue either in various tissue systems or by means of the Kveim test. A compatible clinical or roentgenographic picture without histologic proof was excluded from this analysis; likewise, histologic sarcoid-tissue reactions in the absence of a compatible clinical syndrome were also rejected. The Kveim test was helpful in distinguishing diffuse sarcoidosis from nonspecific local sarcoid-tissue reactions. From an analysis of this series evidence emerged for two forms of sarcoidosis: a transient, subacute type; and a chronic, persistent type. These two forms of the disease differ in many respects, including natural history, response to treatment, and prognosis.

THE CONCEPT OF SARCOIDOSIS[1]

SVEN LÖFGREN

It is quite difficult to discuss the concept of sarcoidosis. In my opinion, for the time being it is impossible to give a final definition because we know nothing about the etiology of the syndrome which we call sarcoidosis. Maybe the pine pollen investigation will throw new light on the etiologic problem, in which case it would perhaps have been better to leave this discussion for the end of our meeting. Granted, however, that the etiology is still obscure, it may be necessary for us to try to define the subject we are going to discuss. In other words, we need to make clear that the syndrome we are discussing is the same in the United States as in Great Britain, Scandinavia, and other countries.

Before I left Sweden to attend this Conference, I was much more convinced of the uniformity of the syndrome than I am today. During these three weeks in Boston, New York, Philadelphia, and Baltimore, I have seen many advanced and severe cases of a type that we very seldom see in Sweden. On the whole, the cases of sarcoidosis that we see in Sweden are of a much milder type, as a rule without the serious complications which I have seen here. I will return to that point later on in the discussion.

One possibility is to base the concept of sarcoidosis on histopathologic criteria. Professor Uehlinger has just given us an outline of the histopathologic features connected with sarcoidosis. As we know, however, the tissue reaction associated with sarcoidosis is rather nondescript. Similar changes are to be found in bacterial infections such as tuberculosis and leprosy, tertiary syphilis, and fungous infections such as coccidioidomycosis, histoplasmosis, and moniliasis, as well as in lesions due to the presence of foreign bodies, among which conditions berylliosis and silicosis should be mentioned.

There are some workers who, despite the nondescript character of the sarcoid lesions, define the sarcoidosis concept on a histopathologic basis. I have in mind especially the school of Scadding. If, in a case of sarcoid lesions, tubercle bacilli are found, Scadding refers to this as tuberculous sarcoidosis. If beryllium poisoning is established, he designates the case as one of beryllium sarcoidosis. If coccidioidomycosis is established, it is considered a case of coccidioidomycosis sarcoidosis. If the etiology is unknown, it is considered a case of sarcoidosis of unknown etiology.

This is a consistent line. The only objection is that, with this view, we lose the clinical aspect of the disease.

Regarding the relationship between histopathologic and clinical criteria in sarcoidosis, I would like here to formulate my opinion. When we assemble all of those conditions associated with a sarcoid tissue reaction of known etiology—tuberculosis, leprosy, tertiary syphilis, fungous infections, and certain foreign body reactions—they form a minority, which, in addition, shows a most variable clinical picture. When, on the contrary, we consider the large majority of cases of sarcoid lesions, we find that the etiology is unknown; and this group with unknown etiology presents numerous clinical features common to many cases, which together just about distinguish the disease as a clinical entity.

Before I give a brief outline of the clinical criteria upon which the diagnosis of sarcoidosis may be based, I want to make two remarks. First, I think that no clinical symptom alone can be considered pathognomonic for sarcoidosis. We must always reckon with a constellation of characteristic symptoms which give us the diagnosis. For the time being, in my opinion, the pulmonary involvement in this respect should be regarded as essential within the clinical picture. We may certainly observe local sarcoid structures in single organs; for example, in a removed cervical lymph node. If otherwise a characteristic clinical picture of sarcoidosis is lacking, so far I feel disinclined to classify the case as sarcoidosis.

Next, I want to emphasize that, in tuberculosis as well as in sarcoidosis, it is important to distinguish between the early and the chronic stages. Primary tuberculosis is one thing and chronic phthisis is quite another. So also in sarcoidosis, the early stage is quite different from the chronic stage. Ten to twenty years ago, it was the general opinion that sarcoidosis was a rare chronic disease, usually with a bad prognosis. At that time we knew very little about the early stage of the disease. Since this stage has now been recognized,

[1] St. Gorans Hospital, Stockholm, Sweden.

we can, on the contrary, say that sarcoidosis is a rather common disease, often with a very good prognosis.

The fact that the primary stage of sarcoidosis has now been recognized is due to two circumstances. First, it has been shown that nodal fever, erythema nodosum, is often a manifestation of sarcoidosis. Fifteen years ago in Scandinavia, primary tuberculosis was the most common cause of nodal fever. Due to the decreasing tuberculosis morbidity, and especially to the rapidly decreasing incidence of primary tuberculous infections, nodal fever of tuberculous origin now is a rare phenomenon in Scandinavia. Instead, sarcoidosis is the most common cause of nodal fever in our countries. Through this knowledge, many new cases of sarcoidosis have been detected, and the clinical picture and prognosis of the early stage have been thoroughly studied.

The group of cases of erythema nodosum has been one source from which we have gained our knowledge of the early stage of sarcoidosis. The second source is quite as important. It is the mass investigations with miniature roentgenograms of the lungs. In these routine examinations, sarcoidosis has been detected in many cases, sometimes at a chronic stage and sometimes at an early stage. For example, a mass investigation of the Stockholm population recently revealed the following figures for the sarcoidosis incidence: for males 3/10,000; for females, 5/10,000. In the age group twenty-five to twenty-nine years, in which the incidence is highest, the rates were 9/10,000 and 11/10,000, respectively.

When we compare the early and the chronic stages of sarcoidosis, the most characteristic picture is no doubt that of the early stage. Most typical are the large bilateral, comparatively symmetric hilar lymphomas, in about one-third of the cases associated with paratracheal lymph node enlargement, usually on the right side. Characteristic is the relative anergy to tuberculin and other bacterial allergens. In most cases of primary pulmonary sarcoidosis there are no subjective or systemic symptoms; therefore, the disease is apt to remain hidden unless the patient undergoes routine chest roentgenography. In certain instances, especially in women, early sarcoidosis is connected with erythema nodosum. Here lactation seems to act as a provoking factor, obviously through hormonal influences. In such a case the picture is usually complicated by fever, painful joints, and elevated erythrocyte sedimentation rate. In about 40 per cent, spotty or patchy parenchymal densities are noted, as a rule not until the hilar lymphomas have begun to diminish. The prognosis of early sarcoidosis is decidedly favorable. About 90 per cent of hilar lymphomas, as well as possibly supervening parenchymal lesions, subside within one or two years.

In the presence of pronounced symptoms, and especially of large hilar lymphomas, the clinical picture of early sarcoidosis will scarcely give rise to confusion with other morbid conditions. The disease most closely resembling primary sarcoidosis with respect to roentgenographic findings seems to be coccidioidomycosis. This condition, however, as you know better than I, occurs only in certain geographic regions. If the lymphomas are smaller, tuberculosis plays the principal part in differential diagnosis.

The pulmonary lesions of the chronic stage (patchy densities, fibrosis, and emphysema) are far less helpful in diagnosis than the lesions of early sarcoidosis. Differentiation from tuberculosis, fungous infections, and pneumoconiosis will sometimes be difficult.

When the pulmonary lesions are nondescript, as in the chronic stage, we must have recourse to the frequently present extrapulmonary changes, several of which are nearly pathognomonic in character. Here I have in mind uveoparotitis, typical sarcoids of mucosae and skin, in particular scar sarcoids, and osseous metastases. Among abnormal findings in the blood, we note hyperglobulinemia in the active generalizing state and, occasionally in conjunction with hypercalcemia, a peculiar disturbance of the renal function.

In all instances, including those clinically typical, we are naturally bound to seek confirmation of our clinical diagnosis by biopsy. Especially in cases that are clinically obscure or doubtful, our task is twofold, namely, to exclude, partly by the means available, other conditions which might have to be considered—tuberculosis, mycosis, pneumoconiosis—and to confirm, partly by biopsy, a diagnosis of suspected sarcoidosis.

However, if I should happen to demonstrate tubercle bacilli in a case in which I have found clinical and histopathologic criteria of sarcoidosis, I would not for this reason necessarily change my diagnosis from sarcoidosis to tuberculosis. I have seen several patients who, in my

opinion, had both diseases at the same time. This interpretation does not appear to me more unreasonable than the simultaneous diagnosis in one patient of tuberculosis and syphilis, or tuberculosis and streptococcal infection, or tuberculosis and silicosis.

The characterization given does not claim to be a precise or final definition of the sarcoidosis concept. As I stated before, for the time being this is an impossibility while the etiologic factor or factors remain obscure. It only provides a provisional but very useful frame for clinical work. As new findings of etiologic importance are obtained, these may necessitate adjustment and probably extension of the limits proposed. Conceivably, certain cases now considered typical will be discarded but, probably or possibly in the future, through demonstration of an etiologic agent, still more cases which at present are regarded as uncharacteristic or uncertain will have to be included in the sarcoidosis group.

At last, a few words on the different types of sarcoidosis in the United States and in Europe, especially in Scandinavia. I think it will be shown this afternoon that there are differences in the clinical picture and prognosis when we compare our patient materials. But for that reason it is not necessary to conclude that we are dealing with two separate diseases. The differences may perhaps be explained by two facts: First, I think the case-finding mechanism is different in the Swedish material than in yours. Most of my patients have been sent to me either because of erythema nodosum or because of an abnormal chest roentgenogram on routine examination. For that reason, the disease very often is in an early stage or there are no subjective symptoms of illness. Most of these patients are examined and treated as ambulants, without hospitalization. I have the impression that sarcoidosis patients in the United States more often consult physicians because of real illness; for example, dyspnea or extensive cutaneous lesions.

The second point is that there may be racial differences. In Sweden we have no Negro population, only white. If the sarcoidosis incidence here is fifteen to twenty times higher in Negroes than in whites, this will indicate that the Negroes afford another soil for the disease than the white population. And I think that this special soil is valid not only for sarcoidosis, but also for other pulmonary diseases; for example, tuberculosis and coccidioidomycosis.

ETIOLOGIC CONCEPT OF SARCOIDOSIS[1]

HAROLD L. ISRAEL

This discussion deals with the problem of whether sarcoidosis is a disease due to a specific inciting agent or whether it is a syndrome which may be caused by a variety of agents. Is everyone talking about the same disorder? Does it have the same cause or causes, here and abroad? Clinical, immunologic, experimental, and epidemiologic evidence may be cited in support of each concept.

Clinical evidence, on the whole, supports a unitarian concept of sarcoidosis. The clinical features, laboratory findings, and natural history of the disease, as observed in English, Swedish, and American studies, are virtually identical, with the few exceptions to be noted. The only notable differences are the greater frequency of erythema nodosum, a more benign course of the hilar adenopathy syndrome in European patients, and a greater frequency of pulmonary fibrosis in American patients; but these variations need not reflect differences in etiology.

With reference to erythema nodosum, I think Dr. Long will comment that every Scandinavian visitor to the Phipps Institute twenty-five years ago had the same question about our failure to recognize erythema nodosum in tuberculosis. It is quite possibly true that we are not as alert to this diagnosis in the United States and perhaps miss occasional cases. However, we have been looking very carefully for erythema nodosum in white patients as well as in Negroes, and we must conclude that it is rare in the United States.

It is worth emphasizing that the diagnostic criteria used in clinical practice are the same in England, Scandinavia, and the United States. The differences of opinion concerning the value of various biopsy techniques or the Kveim reaction are more domestic than international. There is in every series a fringe of cases in which uncertainty exists whether true sarcoidosis or a sarcoid reaction is present. In my judgment, the diagnoses made by Dr. James and Dr. Löfgren are comparable to those that I have made in my patients in the United States.

In many of the cases reviewed together, the judgments were identical regarding the cases which should be included for analysis in the study of sarcoidosis. It is especially impressive that the methods of treatment, the criteria for use of adrenal steroids, and the conclusions as to the value of treatment are identical in these three countries. Surely this unanimity argues for the belief that sarcoidosis is a disease entity which is fundamentally the same in Northern Europeans and North Americans.

Immunologic evidence concerning the nature of sarcoidosis is more equivocal. Many investigators, for example, Rogers and Haserick (1), regard the Kveim reaction as a specific antigen-antibody reaction, and hence consider sarcoidosis a disease entity. Some workers, for example, Kooij (2), believe that the Kveim reaction represents an altered tissue reactivity to particles of a certain size, and conceive of sarcoidosis as a syndrome due to a variety of agents.

Sarcoid granulomas have been induced by implantation of phospholipids, beryllium, silica, and zirconium, and have been observed in many infections. The long list of substances which may evoke a sarcoid reaction has been interpreted as evidence for multiple etiologic factors in sarcoidosis. This inference overlooks a fundamental distinction between sarcoidosis and the sarcoid reaction. Systemic sarcoid lesions have never been experimentally produced by any of the agents which provoke local sarcoid reactions, and not a single case of typical systemic sarcoidosis has been shown to be due to substances which produce local lesions.

The most cogent evidence for the concept that sarcoidosis is a disease entity is epidemiologic. If geographic factors strongly influence the occurrence of sarcoidosis, they can do so in two ways. It is conceivable that some environmental factor alters the host reactivity to provide a "terrain sarcoidique," in which epithelioid granulomas are found in response to a multiplicity of irritants. The experiments of Refvem in Norway (3) and of Hurley and Shelley (4), however, provide powerful evidence against the existence of such a diathesis.

The other fashion in which geographic factors can influence the incidence of sarcoidosis is by exposing the inhabitants of certain areas to environmental substances having the same

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distinctive geographic distribution. This would exclude widely distributed organisms, minerals, and chemicals from consideration as possible etiologic agents. If one is persuaded by the epidemiologic evidence that geographic influences are important in the genesis of sarcoidosis, the belief that sarcoidosis is a syndrome due to a variety of animate and inanimate agents is untenable.

If the epidemiologic observations made in the United States can be substantiated and extended in other countries, strong support will be provided for the concept that sarcoidosis is a specific disease.

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Dr. Long: Dr. Israel has raised a knotty point of distinction between the sarcoid reaction and sarcoidosis, assuming it can be proved that there is an entity. I believe Dr. James called attention to freedom of the adrenal gland from evidence of sarcoidosis. Does everyone agree that the adrenal gland is exempt? Has anyone seen any relation to the treatment of the disease? Dr. Uehlinger, what do you think about the possible incompatibility between the chemical composition of the adrenal gland and the presence of sarcoidosis in the gland?

Dr. Uehlinger: I have never seen a case of generalized sarcoidosis with granulomatous formation in the adrenals. As to the effect of treatment: Without any previous knowledge of the case, I do not think that it is possible to differentiate any specific modifications following therapy.

Dr. Hardy: Has not Dr. Uehlinger made an important point that the noncaseating granuloma of sarcoidosis is the hallmark of what we are talking about, but not necessarily functionally very important? We have had exactly his experience with biopsies before and after treatment of chronic beryllium poisoning. Our pathologists report that, after steroid treatment of beryllium disease, the granulomas may change in number but not in character. And the patient has improved clinically. Not only does he say he has improved, but reversal of lung function and cardiac catheterization abnormalities, and return of serum protein concentrations and spleen size to normal are objective criteria of improvement.

Dr. David Freiman, Professor of Pathology, Harvard Medical School, stresses the importance of the diffuse cellular reaction around the granulomas in this disease as reason for functional impairment.

Dr. Uehlinger: I agree with you, Dr. Hardy. After treatment with steroids, the patient always has a feeling of well-being, of improving. But most of the steroid effects are nonspecific; for example, the normalization of the serum-calcium is a nonspecific effect and has nothing to do with alteration in the granulomas. All we can recognize after treatment with steroids is the disappearance of the lymphatic tissue. By light microscopy, I could not recognize steroid effects in the lung tissue. I would suggest that the improvement of the lung functions is related to the regression of the lymphatic tissue in the bronchial mucosa.

Dr. Siltzbach: I think it would be an oversight if we ended this discussion concerning the histologic changes brought about by steroid therapy in sarcoidosis without some additional comment. On the basis of studying tissues removed by biopsy before and after steroid therapy, it has been shown that striking regressive changes in the epithelioid-cell granuloma occur with treatment in a majority of instances. These regressive changes are observed as early as ten to twelve days after steroids are begun. The literature contains numerous examples illustrating this. Dr. Michael, Dr. Israel, Dr. James, and I, among others, have recorded such examples. The deposit of so-called hyaline or paramyloid material replacing the epithelioid-cell granuloma can be extraordinarily striking. We have found such changes in approximately half the post-treatment tissue biopsies we studied. Therefore, it seems to me that, while the reduction in the number of lymphocytes and other nonspecific inflammatory cells may play an important role in the prompt symptomatic improvement experienced by some patients after steroids are given, the substantial regression of lesions in the lungs, eyes, and skin rests basically upon the shrinkage and resolution of the epithelioid-cell granuloma masses.

Dr. Dunner: Dr. Uehlinger mentioned that in one patient he took biopsies ten years apart, and pointed out that the sarcoid granuloma was of a chronic type and did not change. I am reminded of several cases in which a biopsy was taken and confirmed as compatible with sarcoidosis; the

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clinical picture was that of sarcoidosis. But yet, four or five years later, there was no evidence of sarcoidosis at autopsy. The question I would like to ask is: What is the fate of the granuloma?

DR. UEHLINGER: In my opinion, sarcoid granulomas may disappear without scarring. I would like to add another well known and not very well explained phenomenon. In the course of steroid treatment, the roentgenograms very often show a regression of the hilar lymph nodes. Immediately after stopping steroid treatment, the findings are the same as before steroid treatment. What happens in reality?

DR. SMITH: I would like to speculate a little from the standpoint of an immunologist. It seems to me, in watching my own cases since about 1932, and from what I read and from what I hear, that we might look at sarcoid as an infection which has a point of entrance into the body. A child may get a sarcoid of the eye and have at the onset only lymph nodes on that side of the affected eye. We had one patient who had an injury of the foot; his big lymph nodes were in that leg, with later extension to his lungs. Dr. McKay, of Cleveland, had a Negro nurse who was operated on for appendicitis. Little granulomas were found over the surface of the intestines. The pathologist called it tuberculosis, but there were no pulmonary changes. A year later there were hilar nodes and the miliary picture in the lungs. A review of the original section resulted in the diagnosis of sarcoidosis.

If we consider the etiologic agent entering the body like the tubercle bacillus does, e.g., if it is breathed in, then we should have the enlarged hilar lymph nodes. If it goes into the eye, we would have them beginning in the neck. But, as in tuberculosis, there is a wholesale dissemination with subsequent involvement visible at least at the microscopic level of practically all of the lymph nodes. So, whether it went into the lungs through the mouth by breathing, or through the eye or the tonsil, it is possible to remove a lymph node of normal size from the axilla and yet find this sarcoid picture. This phenomenon is well recognized for tuberculosis.

I am fascinated by the erythema nodosum that occurred in some of the early patients. It does occur here in the United States. I saw a case in Minnesota in a young veteran of the Korean War. An orthopedic surgeon recently described another case to me. One of his neighbors had an interesting type of sarcoidosis. She had joint pains and was referred to the orthopedic clinic. It developed that she had erythema nodosum and that she had lived in a pine forest.

From an immunologic point of view, erythema nodosum appears to me to represent a high degree of allergy of some kind, and that is a curious thing when we think of sarcoid being an anergic disease. I would like to make a plea now that those of you who see these early cases and have the possible chance to make cultures, please instruct your technicians to save the contaminants. We may have been throwing the agent away because we are so conditioned in the laboratories to discard as a contaminant anything we do not recognize. Often it will not even register on the mind. So, if we could get a contaminant from the lymph node, no matter what it is, then we could do what Shiga did originally, which was simply to go back to immunologic tests (such as agglutination or complement-fixation) of the patient's serum.

DR. SILTZBACH: Concerning erythema nodosum and sarcoidosis, there is a test which, in our hands and in the hands of others, does help discriminate between cases of erythema nodosum belonging to the sarcoidosis group and those caused by streptococcal infections and other agents. I refer to the Nickerson-Kveim test. We have had at the Mount Sinai Hospital a number of patients whose sarcoidosis was ushered in by an attack of erythema nodosum combined with symmetrical enlargement of the hilar nodes. We have noted this particularly among Puerto-Rican-born women who, in this regard, appear to be similar to those reported from Sweden by Dr. Löfgren and from England by Dr. James. We performed about two dozen Nickerson-Kveim tests in patients with sarcoidosis at the time when they had erythema nodosum, or shortly thereafter. All the tests, it turned out, were positive. In another small group of patients with erythema nodosum without evidence of sarcoidosis, the Nickerson-Kveim tests were uniformly negative. This high degree of positive response to the Nickerson-Kveim test during the stage of erythema nodosum was also reported by Dr. James, who found more than 90 per cent Kveim-positive in this group.

You may have noted that Drs. James, Löfgren, and Israel all presented the concept that sarcoidosis is a unitary disease of unknown etiology and that it is not, in their opinion, a syndrome. This happens to be my view as well. I would therefore think it appropriate, if this body as a whole shares this view, that the new definition reflect this.

Concerning the bilateral hilar node syndrome, it has been our experience as well that symmetrical enlargement of the hilar nodes is predominantly a finding related to sarcoidosis. Moreover, hilar node enlargement precedes the roentgenographically visible lung involvement. Whenever we have had patients with pulmonary involvement and have been able to obtain previous roentgenograms, sometimes dating back several years, we have

regularly found that the first lesion was not in the lung parenchyma but in the hilar nodes.

Dr. Uehlinger separated the hilar-node phase from the phase of dissemination. There is evidence which indicates that, even in the earliest phases of sarcoidosis, there is already systemic dissemination and, in this respect, early sarcoidosis behaves like primary tuberculosis. In one of Dr. Löfgren's papers concerning the bilateral hilar syndrome, he records 8 patients who had been bronchoscoped and in whom a small portion of pulmonary parenchyma was adherent to the bit of bronchial wall removed on biopsy. Four of these 8 specimens showed granuloma in the lung tissue already present, although a chest roentgenogram disclosed apparently normal lung parenchyma.

We have further evidence of systemic dissemination during early sarcoidosis through findings on needle aspiration of the liver. We have performed liver aspirations in several patients with hilar node enlargement of recent onset and have found the epithelioid-cell granuloma present in the liver tissue. Thus, the lungs and the liver are seeded soon after or simultaneously with the involvement of the hilar nodes.

Dr. Michael: Dr. Smith tells us that sarcoidosis is a disease of "anergy," since the skin does not react. What about Hodgkin's disease?

Dr. Smith: I had better repeat what I said a few minutes ago. I said that the evidence of erythema nodosum in its early stages looks as if there is a high degree of antibody reactivity early in the disease, so we should not consider it a disease of anergy solely because it does not react to antigens later. Does that statement clear it up a bit? As far as we can draw any conclusions from erythema nodosum and tuberculosis, certain bacterial disease, and drug reactions, erythema nodosum represents a high degree of reactivity with some sort of antibody. We do not know how to identify the antibody; we do not know how to test for it.

Dr. James: Dr. Smith is quite right in saying that we should look for antibodies. In the erythema nodosum group, we have endeavored to detect them by precipitin, complement-fixation tests, and agglutination reactions, using sarcoid tissue, pine pollen, tuberculin, and Dr. Nine Choucroun's lipopolysaccharide as antigens. All efforts so far have been fruitless.

I have one further point. We have talked a great deal this morning of the histologic confirmation of sarcoidosis. I suppose we must lean on something for the sake of sanity, but I wonder whether we are leaning too heavily on this evidence, for it may sometimes be flimsy. Dr. Klatskin of Yale University has drawn attention to the lack of specificity of hepatic miliary granulomas. Dr. Clegg of the Brompton Hospital has cast doubt on the specificity of scalene lymph node biopsy, for noncaseous tuberculoid changes may be seen in patients with pulmonary tuberculosis. I have not had much experience or success with blind muscle biopsy, but may not granulomas in muscle also be nonspecific? Are similar granulomas found in muscle biopsies of patients with tuberculosis? Could Dr. Uehlinger tell us which of these three blind biopsies—liver, scalene lymph node, or muscle—is the most reliable?

Dr. Uehlinger: Lymph node tuberculosis and lymph node sarcoidosis cannot be differentiated in most cases. Tuberculosis seldom reaches the scalene lymph node. So, if the clinical picture fits well for sarcoidosis and the biopsy of the scalene lymph node shows a noncaseating tubercle-like granuloma, I suggest the diagnosis of sarcoidosis.

It is much better with muscle biopsies. Muscle biopsies are positive in 10 to 15 per cent. If a muscle biopsy is positive, it proves sarcoidosis, according to my experience. In my thirty years' experience as a pathologist, I have never seen these lesions in the muscle biopsy in cases of tuberculosis. Therefore, I believe, if you have a positive muscle diagnosis, you can be very sure it is sarcoidosis. I visited the Armed Forces Institute of Pathology and looked at what was called sarcoidosis in the United States and compared it with what we call sarcoidosis in Switzerland. We agree completely that it is the same disease and not a different disease.

In answer to Dr. Hardy's question: We did another investigation. We looked up the profession or occupation of 106 persons in military service who had sarcoidosis. We found it very difficult to get a real understanding of what people do in some occupations. It is very difficult to get the atmosphere or the dust composition connected with the occupation. We could not find any sharp or significant relationship between occupation and sarcoidosis among these patients. In 6 patients who were exposed very heavily to dust, a change in occupation was required.

It is my belief that sometimes these nodules within the bronchial mucosa, which lie immediately under the mucosa, may be a result of a reaction to air polluted with dust. I believe that biopsy of the bronchial mucosa is a very useful technique in determining the differential diagnosis.

Dr. James: We must not be left in doubt about this point. You regard a lymph node biopsy as sarcoid when the clinical picture is compatible. Is that correct?

Dr. Uehlinger: Yes, with cervical lymph nodes. However, with scalene lymph node biopsy, the diagnosis can be made independently of the clinical picture.

Dr. James: Do you similarly interpret your

muscle biopsies as sarcoid tissue because the clinical picture is compatible?

DR. UEHLINGER: No. If the muscle biopsy shows epithelioid-cell granuloma without caseation, I think we are authorized to diagnose sarcoidosis.

DR. JAMES: Irrespective of the clinical picture?

DR. UEHLINGER: Yes.

DR. JAMES: You did not mention muscle biopsy in tuberculosis.

DR. UEHLINGER: In autopsy cases of tuberculosis we very often used the muscles of the upper arm and thigh as controls, and we never found tuberculous granulomas.

DR. JAMES: But this is all autopsy material, when autolysis makes it difficult to find them anyway. For the material to be strictly comparable, we should know the results of blind muscle biopsies during life in tuberculous patients.

DR. UEHLINGER: I do not believe so. I have never seen it. We never found any tuberculosis. In cases of sarcoidosis, we have often found muscle biopsy to be positive.

DR. JAMES: It is most important to establish this point. Hepatic granulomas are least evident in late chronic fibrotic sarcoidosis. Likewise, it could be that granulomas are not evident in late fibrotic tuberculosis at the autopsy stage.

DR. UEHLINGER: In liver biopsy it is quite different. It is my belief that it is impossible to differentiate sarcoidosis from tuberculosis from a liver biopsy.

DR. SONES: I wanted to ask Dr. Uehlinger about those 6 cases of dust exposure. What kind of dust?

DR. UEHLINGER: The baking and wood industry.

DR. HIRSCH: From the point of view of the unitary concept of sarcoidosis on an international scale, I would like to dispute slightly Dr. Israel's remarks that the subacute forms of sarcoidosis with bilateral hilar node enlargement of a transient nature are relatively rare in this country and that the chronic forms are more common. This depends, I think, to a great extent on the source of the patients. At the Rockefeller Institute in the past four or five years, we have had most of our patients referred to us from the city Department of Health, and the referrals have consisted largely of cases detected on pre-employment chest roentgenograms and mass chest roentgenographic surveys. In our group, the figures would agree almost exactly with those of Dr. James. In other words, half or more of our patients clearly have subacute or acute—whichever term you want to use—sarcoidosis, with bilateral hilar node enlargement, and these people are well six months to a year after first being detected. They have no symptoms whatsoever.

At New York Hospital, right across the street from us, we have a good control, because the sarcoidosis seen there is almost entirely of the chronic type. These hospital patients are referred for treatment when they become symptomatic and problems arise.

The point that I would like to make is that, in a large general hospital, one sees, I think, an untrue picture of the incidence of sarcoidosis in this country. In the past five years in New York, the Department of Health has done mass chest roentgenographic surveys on large numbers of persons in Negro areas, in one case 50,000 and in another case 80,000. Sarcoidosis was detected in both series at a rate of roughly 1/2,000, which agrees reasonably well with findings in Sweden. In Scandinavia, the chest roentgenogram is used more extensively than here, and physicians are more alert to sarcoidosis than are our physicians in general. Thus, there may not be any real difference in the incidence of the two forms of the disease here and in Europe.

The relative lack of erythema nodosum in this country seems valid and is unexplained. Perhaps it may be a reflection of a high incidence of the disease in Negroes in this country.

This brings us up to a point that will be discussed later in this program, but it seems worth while to emphasize now that any study of the epidemiology of sarcoidosis must take into account the possibility—and, in fact, the probability—that the vast majority of cases of sarcoidosis are never detected. This may be a very common disease, which a large proportion of the population has at some time, but because it is asymptomatic and because it is so transient in nature, it is never detected.

SUMMARY

MAX MICHAEL, JR.[1]

Dr. Long and Dr. Cannan alluded to the Conference on Sarcoidosis in 1948 that was held in this very institution. We were called together by Dr. John Ransmeier, and I believe Dr. Long and Dr. Ransmeier are the only ones of that group who are present today. We deliberated, as I recall,

[1] Jacksonville Hospitals Educational Program, Jacksonville, Florida.

some two days, and one of the major problems was to suggest a definition of sarcoidosis. This was done by splitting off into groups of ophthalmologists, pathologists, radiologists, etc., who finally arrived at a definition about which no one was really very happy. It was a masterpiece of hedging and of veiled language, but I do not know that we have anything better at the moment.

The problem of arriving at a definition may be one of semantics. We talk about disease and syndrome. As I understand it, a disease should have rather characteristic clinical features, which sarcoidosis does have. Its etiology should be apparent, which is not the case for sarcoidosis. The diagnostic criteria should be firm. By that I mean, a specific serologic reaction and/or a histologic pattern which are characteristic. We have been told that we have a characteristic histologic pattern in sarcoidosis. However, we have also been told that this histologic pattern occurs in a variety of other states—we perhaps should use this word and get away from such words as disease and syndrome.

With reference to a syndrome: A syndrome can have all of the above criteria except that there are usually multiple etiologies or no recognized etiology at all. An example of this would be meningitis. If we use the term, meningitis, we are really talking about a syndrome. But then we culture microorganisms from the patient and find we have separated the disease into groups. We might say that meningitis is a syndrome and, when the agents are analyzed, the specific disease becomes apparent.

Then there are other entities in which we all know what we are talking about. We recognize the clinical features; the pathologic features, when present; and perhaps the name; but we have no concept of what the whole thing is about, so we just glorify it by the name "syndrome." This leads me to believe that we are just dealing in semantics.

With specific reference to the presentations, I would like to take exception to Dr. Hardy, if I may, about nomenclature. Let us retain the name *sarcoidosis*. Eponyms are lovely, but we are told to forget them. I like to reconcile this thought with the use of the word "gout," which has absolutely no meaning for the disease. Gout comes from the word "gutta," indicating that the poison has dropped into the toe. This is as far as we can go with gout. So let us retain "sarcoidosis," which really does not tell us a thing. We all know it is not sarcoma, and on that we have agreement. But, if we come up with Hutchinson's name, I am sure that someone will find that ten years before Hutchinson there was another description, and that individual's name should then go to the disease.

One of the problems that has been raised and discussed to a great extent is the "pathologic hallmark." What we need to know is just how characteristic is this hallmark. Is the pathology different in the several stages of the disease? We are now beginning to talk about chronic and acute diseases. Is the pathology the same in the latter as in a chronic and progressive disease? Using the newer techniques, might we uncover more specific information about the histology of the disease? I think Dr. James is quite right in pointing out that we must put an end to such practices as reporting a case of sarcoid of the tongue because something that looks like a hard tubercle was found in the tongue. We must recognize that a variety of things can evoke the sarcoid tubercle, but this does not mean that they all need be called sarcoidosis.

Keeping the two groups in mind, the acute and the chronic and persistent, will be of tremendous help, I think, in further studies of the epidemiology, and particularly of prognosis and treatment, and even perhaps of pathogenesis. I think we are going to find that the clinical features observed in this country and in the European countries are not very different. I agree completely with Dr. Hirsch that the more we look for an acute sarcoidosis, the more we will find it.

In a ten-year survey in Florida of routine roentgenograms of the chest, the incidence of hilar adenopathy greatly exceeded the incidence of what we call classical sarcoidosis. In other words, from roentgenographic reading alone, bilateral hilar adenopathy was observed in many persons. We then come to the problem: If we are to establish clinical criteria, how rigid must these be? We have little or no disagreement on diagnosis in the patient who has uveoparotid fever, disease in his lungs, perhaps bone disease, or skin lesions. The problem arises when we see a patient with scattered granulomas in the lungs which the pathologist says are consistent with sarcoidosis; perhaps the globulin is a bit elevated and the tuberculin may or may not be positive. We have exhausted all current methods of finding a possible etiologic agent. The patient was not exposed to beryllium, he did not come from the histoplasmosis area, so is it sarcoidosis or is it not? If we adopt very rigid criteria for the clinical picture, I am sure we are going to miss many cases. An analogy to this stiuation may be found with myocardial infarction. As for the pathology, we know what causes the necrosis in the myocardium —the coronary artery has been plugged. But we do not know what causes the plug to form. Clinically, the patient may faint and that may be the only manifestation of his infarction. He may show severe, classical chest pain. He may gradually go

into cardiac failure over a period of months. The infarction may be a completely incidental finding at autopsy. No matter which of these conditions existed, the myocardial infarction resulted from occlusion of a coronary artery, and we do not have rigid criteria in diagnosing the disease. True, we have some help in electrocardiographic findings. I am making a plea for us not to be too rigid in our criteria of the nature of sarcoidosis.

There is no question but that more sarcoidosis will be recognized, and I would certainly agree that it is not the rare entity it has been thought to be in the past. A wider variety of clinical pictures will be uncovered. Again, to underline what Dr. James says, just because a sarcoid reaction is found in a single location, let us not call it sarcoidosis. Let us call it the sarcoid reaction. As Dr. Long points out, however, not a sarcoid-like reaction which then means "sarcoma-like-like."

A comparison of acute glomerular nephritis and chronic glomerular nephritis is a good example of the line of reasoning we are trying to pursue. Acute glomerular nephritis is caused by specific strains of streptococci, and recovery is the rule. Chronic glomerular nephritis, the so-called Ellis Type 2, the insidious disease that ends with uremia, according to most investigators, is not the same disease as the acute form. Only the organ which is affected is the same, i.e., the kidney.

Is erythema nodosum with the sarcoid reaction that heals comparable to acute glomerular nephritis, in which there is a specific etiologic agent? Thus, does the sarcoid reaction of erythema nodosum represent an entirely different disease from the more protracted chronic form? I doubt it; we have observations on enough patients who go from the early into the late form.

I have heard much talk today about dissemination of the disease. To me, dissemination connotes something like staphylococci being carried through the body or tumor cells metastasizing around the body. We do not have any evidence that the etiologic agent, whatever it might be, is carried by the blood stream to the liver, to the muscles, or to the lymph nodes. Might this not be a sensitization for which there is some evidence; might not the pathologic findings be the evidence of sensitization? For example, in a case of acute lupus erythematosus, one does not talk about a toxin being carried to the kidneys, to the muscles, to the skin, and so on. It is assumed that all of the blood vessels are involved in this widespread allergic response. So until more is known, I think it is best that we do not use the term dissemination, but refer to the "presence of lesions" in all parts of the body.

It appears that what I have done as a summarizer is add more confusion to what, to me, is a very confusing disease or syndrome. I still think, in many respects, we are dealing with the problem of semantics. We are dealing with an entity the cause of which we do not know, and therein lies the confusion.

I would like to hear two reports as a result of this Conference: (*1*) a definition of what we are defining clinically, and (*2*) a definition of the disease in terms of pathology. How specific is the sarcoid tubercle? Are there any clues to help differentiate the sarcoid tubercle present in this disease from the sarcoid tubercle seen in patients who are exposed to beryllium, the rare individual with histoplasmosis, and so on?

If we have information concerning the clinical features and the histologic features, the diagnosis would be a relatively simple task. I think again, we are all in fairly close agreement on the vast majority of the patients whom we are talking about; we are all talking the same language, as it were. However, it is the occasional case that does not have all of the so-called classic features that evokes so much of the existing confusion.

DR. LONG: Thank you very much, Dr. Michael, for the most encouraging remarks in your discussion. I think your statement is valid that we are all talking for the most part about the same disease. We cannot define it very well; and yet most of us here have a concept of unity in what we are talking about.

RESEARCH ON CLINICAL ASPECTS OF SARCOIDOSIS

D. GERAINT JAMES, *Moderator*

CALCIUM METABOLISM IN SARCOIDOSIS[1]

NORMAN H. BELL, JOHN R. GILL, JR., AND FREDERIC C. BARTTER

INTRODUCTION

Hypercalcemia and hypercalciuria occur frequently in patients with sarcoidosis (1–4). The findings in such patients of an abnormally low fecal calcium which returned toward normal upon the administration of cortisone or its analogues led Henneman and associates (5) and Anderson and co-workers (6) independently to postulate that the syndrome resulted from increased calcium absorption, produced by hypervitaminosis D and by an increased sensitivity to vitamin D, respectively.

An attempt was made to confirm their observations and to investigate further the role of vitamin D in the pathogenesis of the syndrome.

Two patients with sarcoidosis, confirmed by biopsy, one of whom had had kidney stones, underwent balance studies on an air-conditioned metabolic ward. Chemical determinations and the methods employed have been reported previously (7). During the course of the studies, serum antirachitic activity was serially determined by the standard line test (8, 9),[2] in which the serum was fed to rachitic rats.

The response to an increase of calcium intake was measured in each subject and compared with that of the same increase given with vitamin D (10,000 units a day), prednisone (30 to 50 mg. a day), and both vitamin D and prednisone together.

RESULTS

The results are shown in figures 16 to 19.

Effect of increased calcium intake: In *M.C.*, a 43-year-old white woman with a history of kidney stones, an increase of calcium intake (figure 16, days 13 through 24) increased both fecal and urinary calcium and resulted in an elevation of the serum calcium to abnormal values, i.e., above 10.8 mg. per 100 ml.

In *M.E.*, a 20-year-old Negro male, an increase of calcium intake (figure 18, days 13 through 24) increased the mean urinary calcium from normal (138 mg. per day) to abnormal mean values (235 mg. per day) and increased fecal calcium as well, but affected serum calcium little, if at all. There was a positive calcium balance, which was not lost during the subsequent "rebound" (figure 18, days 25 through 36). The hypercalciuria persisted despite subsequent reduction of dietary calcium.

Effect of prednisone and increased calcium intake: In *M.C.*, prednisone (figure 16, days 37 through 48) lowered urinary calcium and increased fecal calcium. Despite a positive calcium balance, there was no rise in serum calcium similar to that seen with increased calcium intake alone. The effect of prednisone persisted during the final twelve-day period, during which the mean urinary calcium was normal (188 mg. per day: figure 16, days 49 through 60).

In *M.E.*, prednisone (figure 18, days 37 through 48) produced no change in either serum or urinary calcium, but there was a marked rise in fecal calcium. During the subsequent twelve days (figure 18, days 49 through 60) urinary calcium fell to normal.

Effect of vitamin D and increased calcium intake: In *M.C.*, vitamin D (figure 17, days 37 through 48) lowered the mean fecal calcium excretion from 730 mg. per day (days 25 through 36) to 144 mg. per day (days 49 through 60), increased mean urinary calcium excretion from 143 mg. per day (days 25 through 36) to 293 mg. per day (days 49 through 60), but did not affect the elevated serum calcium concentrations.[3]

In *M.E.*, vitamin D lowered fecal calcium (compare figure 19, days 13 through 24 with figure 18, days 13 through 24). There was no significant change in either urinary or serum calcium.

Effect of prednisone and vitamin D and increased

[1] From the Clinical Endocrinology Branch, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

[2] Performed by the Division of Nutrition, Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D. C.

[3] A single value of 14.4 mg. per 100 ml. on day 47 could not be verified and is probably an error.

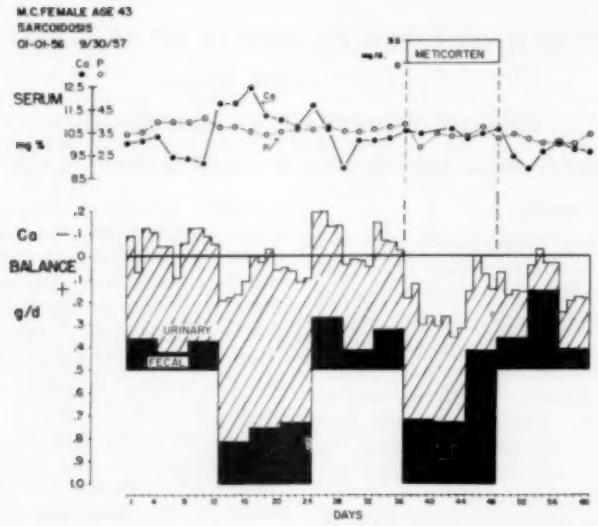

FIG. 16. The effect of increasing calcium intake and of prednisone (Meticorten®) on serum calcium and phosphorus and calcium balance. Note the low fecal calcium and marked hypercalciuria during the first twelve days of the study. In this and subsequent figures, calcium intake is plotted from the zero line to the bottom of the column, and urinary and fecal calcium values are plotted upwards from the intake line. Thus, a positive balance is shown as a clear area below the line, a negative one by fecal or urinary values above the zero line.

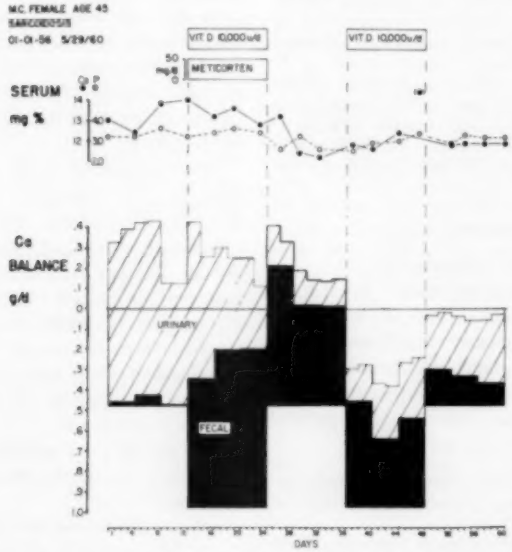

FIG. 17. The effect of increasing calcium intake and vitamin D alone and in combination with prednisone (Meticorten®) on serum calcium and phosphorus and calcium balance.

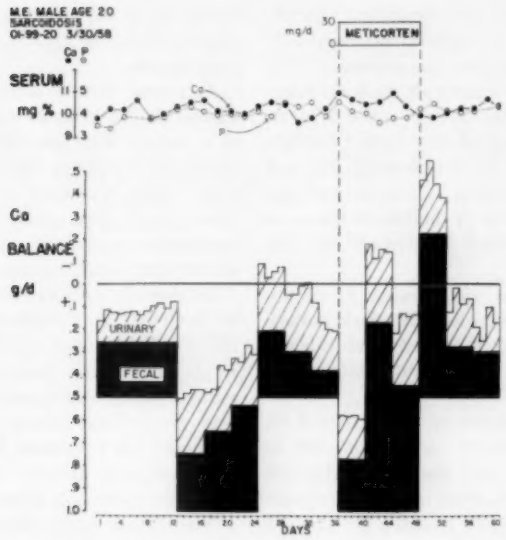

FIG. 18. The effect of increasing calcium intake and of prednisone (Meticorten®) on serum calcium and phosphorus and calcium balance. Note that urinary calcium became abnormally elevated only after the calcium intake was increased (days 13 through 24), and that this effect persisted during the subsequent twelve days, even though the calcium intake was reduced.

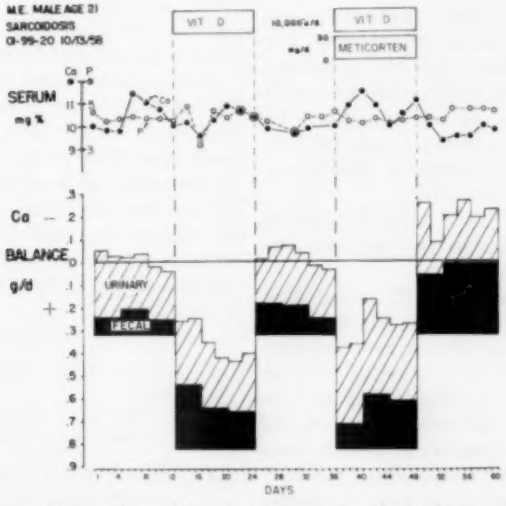

FIG. 19. The effect of increasing calcium intake and vitamin D alone and in combination with prednisone (Meticorten®) on serum calcium and phosphorus and on calcium balance. Note that the serum calcium in this patient was intermittently elevated independently of calcium intake and medication

calcium intake: In *M.C.*, prednisone and vitamin D (figure 17, days 13 through 24) produced: (*1*) a fall in mean urinary calcium excretion from 751 mg. per day (days 1 through 12) to 143 mg. per day (days 25 through 36), (*2*) a rise in mean fecal calcium from 47 mg. per day (days 1 through 12) to 730 mg. per day (days 13 through 24), and (*3*) a fall in serum calcium. These changes are similar to those produced by prednisone alone, as shown in figure 16 (days 37 through 48, *vide supra*).

In *M.E.*, prednisone and vitamin D (figure 19, days 37 through 48) did not affect urinary and serum calcium but increased fecal calcium (compare with effect of each drug alone, *vide supra*).

During the studies shown in figures 16 and 19, serum antirachitic activity varied from 100 to 350 units per 100 ml., and thus was within the range which we have observed in normal persons. Similar findings have been reported by Thomas and co-workers (10).

Discussion

These studies indicate that patients with sarcoidosis and hypercalciuria may have abnormally low fecal calcium, that prednisone may increase the fecal while lowering the urinary calcium, and that vitamin D in low doses has the reverse effect. Furthermore, prednisone can prevent or reverse the action of vitamin D. The data are thus consistent with the hypothesis that the hypercalciuria in this syndrome results from hyperabsorption of calcium; that the hyperabsorption results from a hypersensitivity to vitamin D; and that prednisone acts by opposing this action of vitamin D.

Several investigators have reported results of calcium balance studies in patients with sarcoidosis and hypercalciuria.

Henneman and associates (5) noted that increasing calcium intake in two patients moderately increased urinary calcium, increased fecal calcium, and produced either a positive or a less negative calcium balance. Similar findings were also reported in three patients by Jackson and Dancaster (3). These results agree with those obtained in the patients here reported and indicate that the increased absorption of calcium with resultant hypercalciuria and hypercalcemia is in part dependent on calcium intake.

Treatment with cortisone (2, 3, 5, 6, 11), hydrocortisone (5), and prednisone (3) has generally shown, as in our patients, a reduction in serum calcium, a fall in urinary calcium, and a rise in fecal calcium.

Anderson and co-workers (6) administered calciferol (10,000 units per day for twelve days) to a patient with sarcoidosis without producing significant change in either urinary or fecal calcium values. Cortisone (100 to 150 mg. daily) when given with calciferol for eighteen days produced a rise in fecal calcium and a fall in both urinary and serum calcium.

Mather (2) gave calciferol (10,000 units daily for twelve days) to a patient with sarcoidosis, and noted a fall in fecal calcium and a rise in both serum and urinary calcium from normal to abnormal values. When cortisone (150 mg. per day) was given concomitantly, the serum calcium gradually fell to normal, fecal calcium gradually increased, and urinary calcium rose and then gradually decreased, albeit not to normal values.

The normal serum antirachitic activity in our patients suggests that the increased calcium absorption was due to an increased sensitivity to vitamin D rather than to an excess of the circulating vitamin.

Summary

Balance studies were performed on 2 patients with sarcoidosis and hypercalciuria. Extra calcium was given alone, with prednisone, with vitamin D, and with both drugs together.

Both patients showed low fecal calcium values, further lowered by vitamin D and raised by prednisone; with both drugs together, the prednisone effect predominated. Serum vitamin D concentrations were normal in both patients.

These and other published data are interpreted to support the view that hypersensitivity to vitamin D, reversible with corticoids, is a cardinal feature of the syndrome.

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STUDIES OF THE PRODUCTION, VOLUME, AND DESTRUCTION OF ERYTHROCYTES IN PATIENTS WITH SARCOIDOSIS[1, 2]

MARTIN E. LIEBLING,[3] NORMAN H. BELL, AND JAMES M. STENGLE
(With the technical assistance of Irene Clark)

Introduction

Previous studies in patients with diseases characterized by chronic inflammation have shown abnormalities in both iron metabolism and erythrocyte life span. Patients with acute rheumatic fever may have a shortened erythrocyte life span (1). Patients with chronic infection or rheumatoid arthritis have been shown to have anemia (2–9), hypoferremia (8–11), and a normal (5–7) or shortened (3, 4, 8, 12, 13) erythrocyte life span.

It is the purpose of this report to present an investigation of the iron metabolism and apparent erythrocyte life span in patients with sarcoidosis.

Methods

Two groups of patients were studied. One was composed of 13 male and 19 female patients, 28 of whom were Negro. Twenty-eight of the group had the clinical diagnosis confirmed by biopsy. In the remaining 4 patients, the diagnosis was not confirmed by biopsy. The patients had no demonstrable infection and no evidence of sicklemia, impaired renal function, or history of recent blood loss. Serial serum iron and total iron-binding capacity were obtained in this group at four-hour intervals. (The 4 a.m. sample was omitted.) Similar determinations were obtained in a group consisting of 11 male and 11 female normal adults ranging in age from twenty-two to fifty-three years. The total iron-binding capacity was not obtained in one normal male patient. A second group composed of 13 Negro patients was studied with Fe^{59} and Cr^{51} (*vide infra*). In each of these patients, the diagnosis was confirmed by biopsy. The same criteria for selection were used with the following exceptions: *H.S.* was found to have sickle cell trait, reduplication of the left ureter, and a history of unilateral hematuria; *E.B.* was found to have a low-grade pyelonephritis and normal renal function, as evidenced by normal blood urea nitrogen and phenosulfonphthalein excretion test. All patients had had clinical evidence of sarcoidosis for at least two years. Eight of the 13 subjects had pulmonary symptoms, for which 5 had received steroids (table 6).

The hematocrit of heparinized venous blood was measured in duplicate by the capillary tube technique (14), hemoglobin was measured by the cyanmethemoglobin method, erythrocyte counts were performed using a Coulter counter (15), reticulocyte counts were performed with the method of Brecher (16), and serum iron and total iron-binding capacity were measured by the method of Schade and co-workers (17).

Plasma and erythrocyte Fe^{59} turnover were measured by the method of Huff and associates (18). Approximately 10 μc of Fe^{59} of high specific activity was incubated with 30 ml. of the patients' heparinized whole blood; in no case was the iron-binding capacity exceeded. The total circulating erythrocyte volume was determined by a modification of the method of Read (19). Approximately 100 μc of Cr^{51} of high specific activity were incubated with the patient's whole blood; the excess of Cr^{51} was reduced with 50 mg. of ascorbic acid. Plasma volume and total blood volumes were calculated from the total erythrocyte volume and venous hematocrit. Apparent erythrocyte survival was estimated by the method of Ebaugh and associates with Cr^{51} (20). Two-milliliter aliquots of each sample were counted in a well-type thallium-activated sodium iodide crystal scintillation counter. Body surface scanning of liver, spleen, and sacrum for Fe^{59} and liver and sacrum for Cr^{51} were performed by the method of Elmlinger and associates (21) with a thallium-activated sodium iodide crystal with correction for decay and activity of the circulating blood (8).

Results

Studies of serum iron and total iron-binding capacity: Significant hypoferremia ($P < 0.01$) was present in one group of 32 patients with sarcoidosis when compared with a group of 22 normal subjects (figure 20). A diurnal-nocturnal variation in mean serum iron occurred and was not present in every case (22). The difference in mean total iron-binding capacity between the patients and normal subjects was not significant (figure 20).

Studies with Fe^{59} and Cr^{51}: Results are shown in table 6 and figure 21.

[1] From the General Medicine Branch, National Cancer Institute; and the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

[2] Because of time limitations, this paper was not read at the Conference. However, it was summarized during the discussion period and, for completeness, is included here.

[3] Present address: Department of Medicine, Durham Veterans Administration Hospital, Durham, North Carolina.

TABLE 6

SUMMARY OF Fe^{59} TURNOVER AND CR^{51} ERYTHROCYTE METABOLISM STUDIES

Name	Age	Sex	Weight	Hemoglobin	Hematocrit	Mean Serum Iron*	Initial Serum Iron†	Plasma Fe^{59} $T_{\frac{1}{2}}$	Erythrocyte Fe^{59} Uptake	Fe^{59} Erythrocyte Turnover	Blood Volume	Plasma Volume	Erythrocyte Volume	Cr^{51} Erythrocyte Survival $T_{\frac{1}{2}}$	Remarks
	years		*kg.*	*gm. per 100 ml.*	*per cent*	*γ per 100 ml.*	*γ per 100 ml.*	*hours*	*per cent*	*mg./kg./day*	*ml./kg.*	*ml./kg.*	*ml./kg.*	*days*	
Normal values mean:				14.0	42.0		98	1.51		0.27	59.1	34.0	23.9	29	
Female range:				12.0	37.0		43	1.05		0.18	40.0	26.6	19.3	23	
				16.0	47.0		175	2.33		0.37	85.0	46.6	32.7	40	
M.T.	38	F	57.0	13.2	40.0	63	58	1.25	85.2	0.22	47.6	29.5	18.1	34	
I.G.	41	F	89.0	13.3	40.0	49	59	1.40	100.0	0.21	46.7	28.7	18.0	28	
G.S.	27	F	46.5	12.4	37.0	42	59	1.28	84.1	0.24	55.5	35.0	20.5	26	
C.W.	59	F	59.3	13.0	41.0	51	44	0.85	89.2	0.25	53.9	31.8	22.1	26	
E.B.	24	F	85.2	13.5	43.0	64	84	0.93	97.7	0.32	39.8	21.9	17.9	29	Prednisone 7.5 mg./day
B.W.	37	F	87.5	13.2	39.5	—	94	1.72	80.7	0.19	41.8	24.0	17.8	27	
M.F.	35	F	44.6	12.2	40.0	33	22	0.70	88.2	0.18	62.8	37.4	25.4	27	
G.O.	40	F	59.9	14.8	46.5	42	66	0.90	100.0	0.45	68.6	36.3	32.2	34	Prednisone 5.0 mg./day
C.McD.	14	F	24.7	11.2	37.0	34	32	0.30	79.0	0.57	64.3	38.6	25.6	30	
L.B.	27	F	52.3	13.0	40.0	—	77	1.15	77.8	0.39	68.0	39.0	29.0	26	Prednisone 7.5 mg./day
Normal values mean:				16.0	47.0		100	1.51		0.33	65.5	36.7	29.6	29	
Male range:				14.0	40.0		56	1.05		0.26	40.0	23.1	20.0	23	
				18.0	52.0		206	2.33		0.43	105.0	44.6	39.7	40	
H.S.	36	M	84.3	16.0	47.5	—	94	1.10	92.2	0.42	61.8	31.8	30.0	27	Sickle cell trait with hematuria
W.B.	28	M	59.2	14.9	44.0	56	62	0.95	72.9	0.26	66.3	37.0	29.3	26	
H.C.	36	M	73.5	14.3	44.0	37	52	0.85	92.6	0.29	52.3	30.9	21.5	26	Off prednisone for one month

* Serial values during 24-hour period

† Obtained at the time of intravenous injection of Fe^{59}

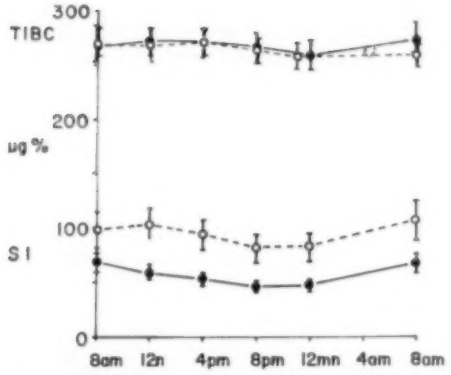

FIG. 20. Mean serum iron (SI) and total iron-binding capacity (TIBC) values obtained serially over a 24-hour period in 22 normal subjects and in 32 patients with sarcoidosis.

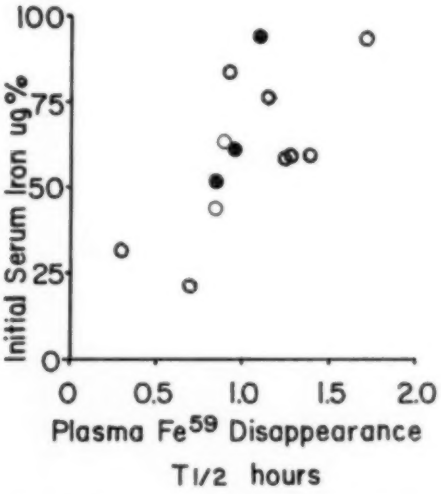

FIG. 21. Correlation of plasma Fe^{59} disappearance half-time with initial serum iron in 13 patients with sarcoidosis. Females are plotted as white circles; males as black circles. Correlation is significant (r equals 0.828, $P < 0.001$).

Although hemoglobin and hematocrit values in the 13 patients were generally within the normal range (23), 4 of the patients (*M.T.*, *I.G.*, *E.B.*, and *B.W.*) had abnormally low Cr^{51} erythrocyte volume determinations. The low values in 3 of these subjects (*I.G.*, *E.B.*, and *B.W.*), each of whom weighed more than 85 kg., perhaps can be attributed to obesity (24). In 2 other patients (*G.S.* and *H.C.*) these values were low normal (24–35).

Three patients who did not show a reduction of erythrocyte volume (*G.O.*, *C.McD.*, and *L.B.*) had pulmonary fibrosis. All had elevated erythrocyte Fe^{59} turnover values; 2 (*G.O.* and *L.B.*) had high normal total erythrocyte volumes (table 6). *G.O.* had the alveolar-capillary-block syndrome; the arterial oxygen saturation varied from 70 to 80 per cent.

In all patients, the Cr^{51} apparent erythrocyte life span determinations were normal (36), and reticulocyte counts were less than 1.5 per cent.

Four of the patients had abnormally low initial serum iron values; 9 had abnormally shortened plasma Fe^{59} disappearance half-times (3, 8, 18, 37) (table 6). In all patients, initial serum iron and plasma Fe^{59} disappearance half-time determinations correlated significantly (figure 21).

Body surface counting was performed in 6 patients (*C.McD.*, *M.T.*, *C.W.*, *I.G.*, *G.S.*, and *W.B.*). In a typical study (figure 22), injected plasma-labeled Fe^{59} was rapidly taken up and released from the sacral area and incorporated at a normal rate by peripheral erythrocytes.

DISCUSSION

The findings indicate that hypoferremia occurs frequently in patients with sarcoidosis, that injected transferrin-labeled Fe^{59} may be removed from plasma at a rate more rapid than normal, and that Fe^{59} incorporation into erythrocytes is normal.

A number of studies have suggested that anemia, heretofore generally defined as an abnormally low hemoglobin or hematocrit, may be more precisely defined as an abnormally low total erythrocyte volume. Both Berlin and associates (38) and Hollingsworth and Hollingsworth (7) found decreased total erythrocyte volumes in patients with active pulmonary tuberculosis. They showed that the venous hematocrit was not a reliable index of anemia. Crosby (25) demonstrated a greater reduction in Cr^{51} erythrocyte volume than in venous hematocrit in patients with various types of anemia. Since the hematocrit may be altered by changes in plasma volume, decreases in plasma volume may obscure the presence or degree of anemia.

Six of the 13 patients in the present study had either low or low normal erythrocyte volumes; 3 of these patients were obese (*vide supra*). Since

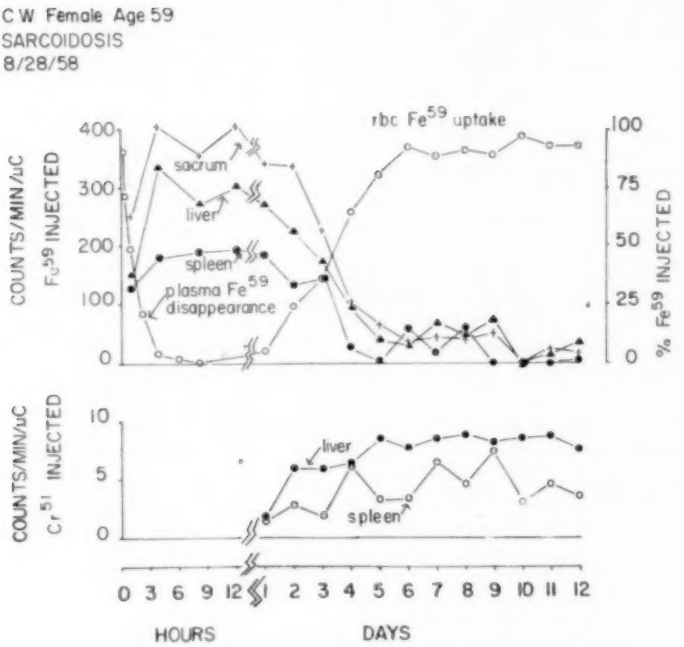

FIG. 22. Body surface counts of Fe^{59} and Cr^{51} over the liver, spleen, and sacrum, with plasma Fe^{59} disappearance and erythrocyte Fe^{59} uptake in a patient with sarcoidosis.

low erythrocyte volumes may be associated with obesity, in only 3 patients can a low total erythrocyte volume be attributed to sarcoidosis. Unlike patients with tuberculosis, however, the group showed no tendency to have low erythrocyte volumes.

Because both erythrocyte Fe^{59} turnover values and Cr^{51} apparent life span determinations were not abnormally low in any of the patients, no mechanism for the low erythrocyte volumes was evident.

In a recent study (39), Fe^{59} turnover and Cr^{51} erythrocyte apparent life span were determined before and during treatment with amphotericin B, an antifungal drug known to produce anemia. Although amphotericin B produced an average fall of 2 mg. per 100 ml. in hemoglobin concentration in 20 of the 29 patients, the changes in Fe^{59} turnover and Cr^{51} apparent erythrocyte life span were not great enough to account for the anemia. Thus, although each patient served as his own control and the drug produced anemia, the mechanism (hemolysis or decreased erythrocyte production) could not be defined. This suggests, as does the present study, that these determinations measure only gross changes.

An explanation for the hypoferremia associated with inflammation has been offered by Freireich and associates (40). They postulate a defect in the release of iron by the reticuloendothelial system. Weinstein (6) was unable to demonstrate any such defect in a single patient with rheumatoid arthritis. He was also unable to demonstrate any abnormality in Fe^{59} gastrointestinal absorption in a number of such patients.

In contrast to patients with chronic infection, who have been shown to have a low total iron-binding capacity (9), the mean total iron-binding capacity of a group of patients with sarcoidosis herein reported was not significantly different from that of a group of normal persons (*see* figure 20).

The results of the present studies of iron metabolism and erythrocyte volume and survival are remarkably similar to those obtained in patients with chronic infection (7, 8), rheumatoid

arthritis (3, 5, 6), cancer (41), and patients treated with amphotericin B (39). A notable exception is that in none of the patients in the present study could hemolysis be demonstrated.

Summary and Conclusions

The mean serum iron was found to be abnormally low in a group of 32 patients with sarcoidosis. The mean total iron-binding capacity was normal.

Six of 13 patients so studied had low or low normal Cr^{51} total erythrocyte volume determinations; Cr^{51} apparent life span was normal in each of the 13 patients. Since Fe^{59} erythrocyte turnover values were not abnormally low, no cause for the low erythrocyte volumes was apparent.

Body surface counting of Fe^{59} and Cr^{51} in 6 patients so studied was normal.

The findings appear not to be specific for sarcoidosis, but are similar to those found in other diseases associated with chronic inflammation.

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OCULAR ASPECTS OF SARCOIDOSIS[1]

LORENZ E. ZIMMERMAN AND A. EDWARD MAUMENEE

I. Clinical Findings[2]

The eye and its adnexa are frequently involved by lesions of sarcoidosis. Fisher (1) reported that ocular changes were present in 40 per cent of 122 patients with this disease and Colover (2) noted iridocyclitis in 67 of 118 cases of sarcoidosis. Frequently the ocular lesions are the first clinical manifestations of the disease.

A list of the clinical manifestations of sarcoidosis, as they appear in and about the eye, is presented in table 7. The skin lesions consist of small millet-seed, clear nodules or, occasionally, larger masses near the border of the lid that resemble chalazions.

Involvement of the lacrimal gland may manifest itself in two ways. The most common is an infiltration of the glandular tissue which produces a nonpainful firm, hard, swollen mass in the area of the lacrimal gland. Such changes are frequently bilateral, and may be accompanied by similar swelling in the area of the parotid gland. They occur in patients with generalized sarcoidosis. The second type of lacrimal gland involvement is manifested by a lack of tears. This produces a dry eye, mucous secretion, superficial punctate erosion of the conjunctiva and cornea. The ocular picture produced from this lesion is similar to that seen in keratitis sicca associated with Sjögren's disease.

Nodular areas of infiltration may occur in both the bulbar and palpebral conjunctivae. When the lesions occur in the palpebral conjunctiva they frequently simulate the elevated papular masses of vernal conjunctivitis. Some patients show large cervical nodes along with changes in the conjunctiva. Nodular, fleshy-appearing masses may also occur in the bulbar conjunctiva or episcleral area.

Very, very rarely a patient shows involvement of the bulbar conjunctiva; the nummular type, that with small lesions which are ill-defined in the stroma, can occur. These lesions respond rather rapidly to therapy.

The cornea is frequently involved with opacities and edema secondary to anterior uveitis. On rare occasions nummular-like opacities may develop in the stroma with very little evidence of anterior uveal inflammation. Another very unusual complication is a primary band keratopathy that results from the hypercalcemia of systemic sarcoidosis.

The most frequent ocular involvement of sarcoidosis is an anterior uveal inflammation. This may begin as a low-grade nongranulomatous type inflammatory response that very quickly changes to a granulomatous reaction, evidenced by mutton fat keratic precipitates, nodular elevations in the iris (Bassaca nodules), and masses of epithelioid cells (Koeppe nodules) at the pupillary borders. The inflammatory reaction is chronic in nature and frequently causes secondary changes in the anterior segment of the eye. The most common of these are peripheral and anterior synechiae, destruction of the iris stroma, secondary glaucoma, and cataract (3).

Vitreous opacities are usually present in patients with anterior uveal inflammation. These changes are nonspecific in nature. In some cases small globular masses may be noted in the inferior portion of the vitreous just in front of the retina. When such lesions occur without other involvement of the vitreous or little evidence of

TABLE 7

Clinical Manifestations of Sarcoid in the Eye and Adjacent Structures

1. Millet-shaped nodules in the skin and pseudo chalazions
2. Enlargement of the lacrimal glands
3. Keratitis sicca
4. Nodular infiltrates of the palpebral conjunctiva
5. Nummular and band-shaped calcification of the cornea
6. Episcleral nodules
7. Iridocyclitis
8. Nodular vitreous opacities
9. Retinitis
10. Choroiditis
11. Optic neuritis
12. Orbital tumors
13. Paralysis of the extraocular muscles
14. Visual field defects

[1] From the Armed Forces Institute of Pathology, Washington, D. C.; and Wilmer Ophthalomological Institute, Johns Hopkins University and Hospital, Baltimore, Maryland.

[2] Read by Dr. Maumenee.

FIG. 23. The anterior chamber on one side is largely filled by the massive proliferation of epithelioid cell tubercles in the iris. (AFIP accession 71412, × 6)

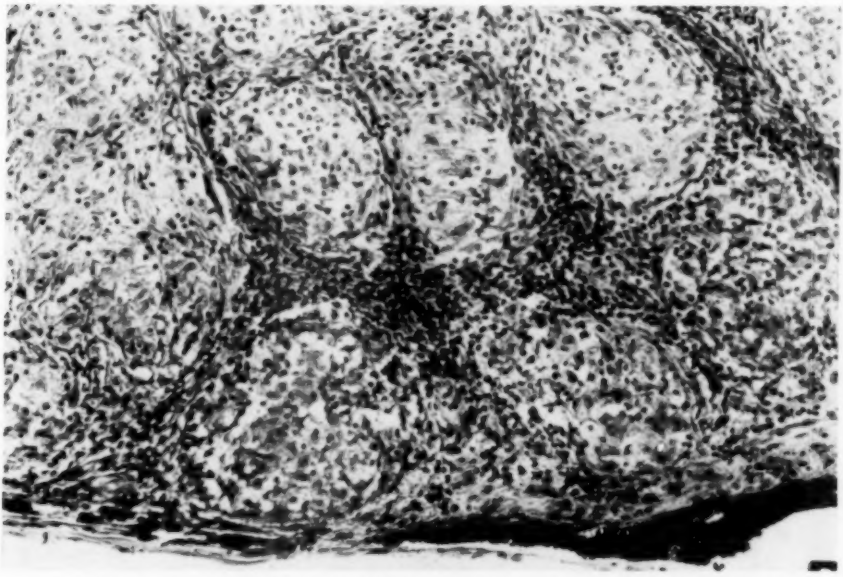

FIG. 24. Discrete noncaseating epithelioid cell tubercles in iris of same case of sarcoidosis shown in figure 23. (× 350)

anterior uveal involvement, they are usually indicative of sarcoidosis.

In contrast to the frequency with which the anterior uveal segment is involved, lesions of the retina and choroid are rare. Small white opacities have been noted in the retina and on the surface of the retinal blood vessels and, occasionally, a true choroidoretinitis of a granulomatous type is found in patients with systemic sarcoidosis.

Edema and hyperemia of the optic disc have been noted by Colover (2) in 26 of 118 cases. Marked inflammation of the optic nerve, however, is very rare. On occasions, an exudative reaction can be seen on the surface of the disc, and in others retrobulbar inflammatory lesions produce a marked loss of visual acuity.

The hard tubercles of sarcoidosis have been known to simulate orbital neoplasms. Occasionally, the inflammatory mass may be located in an extraocular muscle and may produce a paralysis of this organ. More frequently, however, the extraocular muscle palsies are of more central origin. Walsh (4) states that facial paralysis usually occurs as a result of involvement of the parotid gland. However, he has noted a seventh nerve palsy in the absence of parotitis.

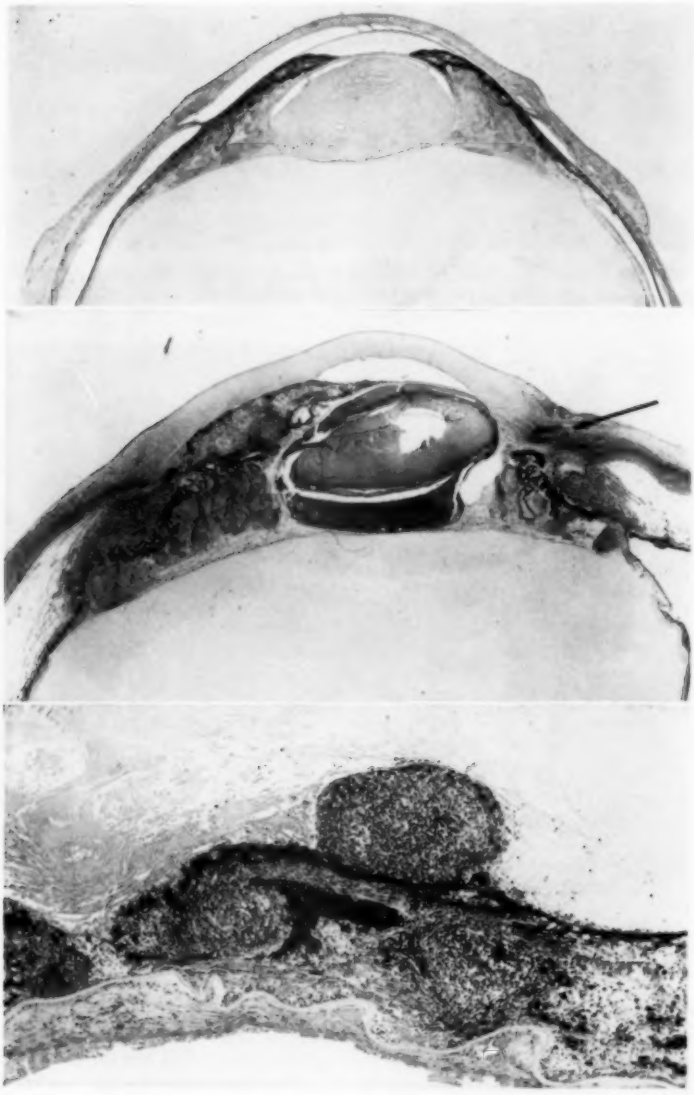

FIG. 25 (Top). The anterior chamber is almost obliterated by the broad anterior synechias, while the posterior chamber is filled by the granulomatous inflammatory tissue largely derived from the ciliary body. There are also broad adhesions of the iris to the lens. (AFIP accession 289584, × 6)

FIG. 26 (Center). In this case the changes are similar to those shown in figure 25. In addition, there are epithelioid cell tubercles in the iridectomy scar at the limbus (arrow). (AFIP accession 165628, × 9)

FIG. 27 (Bottom). Epithelioid cell tubercles project from both surfaces of the iris and there are dense fibrous adhesions of the iris to the cataractous lens. (AFIP accession 314151, × 48)

Visual field defects may occur as a direct involvement of the optic nerve, meningeal sheaths, pituitary gland, or the brain.

From the ophthalmologist's point of view, the most important lesions in sarcoidosis are the intraocular changes. Not only is anterior uveitis the most frequent lesion in the eye and adnexa, it is also the most destructive of vision. Intraocular inflammation of recent onset in patients with systemic sarcoidosis usually responds favorably and rapidly to systemic steroid therapy. When the hormone therapy is discontinued, the uveal inflammation may recur. If the intraocular inflammation has been allowed to become chronic,

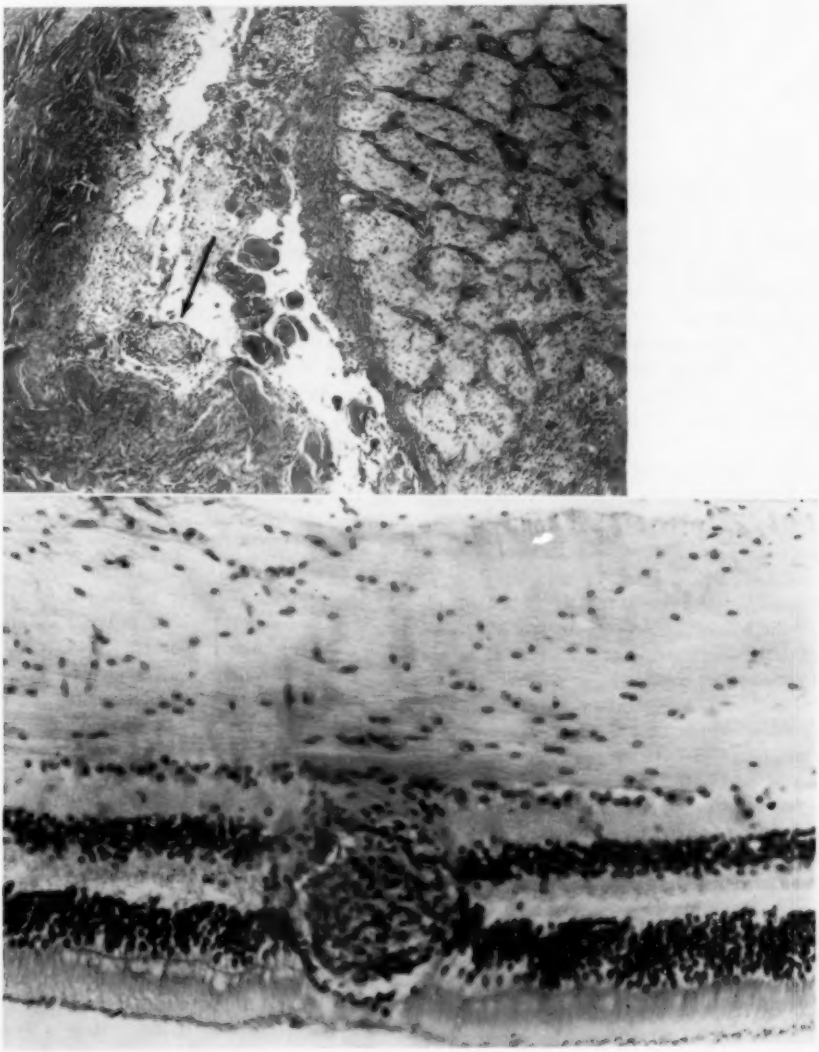

FIG. 28 (Upper). Minute epithelioid cell tubercle in meninges of optic nerve (arrow). (AFIP accession 316231, × 53)

FIG. 29 (Lower). Epithelioid cell tubercle in retina. (AFIP accession 71412, × 330)

FIG. 30. Granulomatous choroidoretinitis due to sarcoidosis. Large posterior segment lesions of this type are unusual in sarcoidosis. (AFIP accession 733320, × 20)

or if it is extremely severe, the response to massive doses of steroids is frequently undetectable.

In summary, the granulomatous inflammatory lesions of sarcoidosis frequently involve the eye and its adnexa. Almost all tissue in this area is susceptible to these lesions.

II. HISTOPATHOLOGIC FINDINGS[3]

The histopathologic features of most of the lesions that Dr. Maumenee has described are essentially similar to those seen in other tissues (figures 23 and 24).

I would like to describe to you, at the outset, some of the intraocular lesions that we have seen in eyes that have come to enucleation. The main complication that leads to loss of the eye by surgical removal is secondary glaucoma. This complication, which may lead to blindness, is often accompanied by such discomfort that the eye has to be treated by enucleation. We have seen a few cases in which problems in differential diagnosis also have led to enucleation. One very unusual case concerned a young Negro male who had been struck in the eye a few weeks before being seen. The injured eye became inflamed, and through fear of sympathetic uveitis, the eye immediately was removed. Lesions were found that were entirely different from those seen in sympathetic uveitis, but were indicative of sarcoidosis. This case is unusual; ordinarily it is secondary glaucoma that brings the eye to the pathology laboratory. The reason that these patients develop secondary glaucoma, as Dr. Maumenee pointed out, is that the lesions usually involve the anterior segment.

Seen histologically, the large massive confluent groups of epithelioid tubercles are developed principally from the iris and ciliary body. In some cases, much of the anterior chamber is filled by the granuloma which lies against the cornea (figure 23). In other cases the anterior chamber is largely obliterated by anterior synechias (figures 25 and 26). A good deal of the circumference of the anterior chamber is often involved. The outflow of aqueous from the anterior chamber via the chamber angle is blocked.

The lesions are not always massive. The granulomas project from either the anterior or the posterior iris surface (figure 27). Often they are associated with the development of an exudate that seals the iris to the anterior surface of the lens, obstructing outflow of aqueous from the posterior chamber through the pupil into the anterior chamber (figures 25–27).

Extensive lesions often involve the ciliary body. Sometimes the disease completely involves the iris or ciliary body along the entire circumference of the anterior segment. Massive lesions are sometimes seen projecting from the ciliary processes, filling up the entire posterior chamber. Everything anterior to the vitreous body becomes filled by the granulomatous inflammatory tissue (figures 25, 26).

An interesting feature seen in a few cases in

[3] Read by Dr. Zimmerman.

which surgical procedures have been performed on the eye is the development of granulomas within the surgical scar (figure 26). The posterior segment, as Dr. Maumenee has pointed out, may be involved, but in the histopathologic material which we have had an opportunity to study, usually very small tubercles are seen which are rarely significant. Small granulomas may be seen in the parenchyma or meninges of the optic nerve (figure 28), in the retina (figure 29), or in the choroid. Ordinarily they are tiny lesions, of no clinical significance, found incidentally in eyes that were removed because of extensive involvement of the anterior segment.

As Dr. Maumenee pointed out, we do occasionally see clinically significant posterior segment lesions. For example, we have seen lesions on the inner surface of the retina with involvement of the vitreous body by this same granulomatous process. There are lesions that lead to a localized retinal detachment and focal lesions involving the posterior segment. We have seen choroiditis with granulomas in the choroid erupting through Bruch's membrane to involve the retina and vitreous (figure 30). Just such a picture was seen after enucleation in a patient who subsequently died of his systemic sarcoidosis (figure 30).

I would like to present at this time one problem in differential diagnosis that we who practice ophthalmic pathology are confronted with now and then. Dr. Maumenee pointed out the granulomatous lesions that may occasionally be seen on the eyelids. A granulomatous process affecting the lids, which is very much more common than sarcoidosis, is the chalazion, an infection and obstruction of the Meibomian glands in the tarsal plate. Usually this can be differentiated from sarcoidosis with ease. Little fat droplets surrounded by polymorphonuclears are found in the center of the granulomas (figure 31). Occasionally, epithelioid tubercles predominate, and then the lesion may be misinterpreted to be due to tuberculosis or sarcoidosis. It is interesting, I think, to point out that some of the inclusions described by Dr. Uehlinger in the earlier session as especially characteristic of sarcoidosis may be seen in these chalazia also. We have seen laminated basophilic Schaumann bodies within the epithelioid and giant cells (figure 32). With polarized light, birefringent crystalloids can be seen which might not be seen with ordinary light. At times, one may even see typical asteroid bodies in chalazia (figure 33). It must be remembered, however, that none of these special microscopic features which are used as aids in the histopathologic diagnosis of sarcoidosis may be considered pathognomonic because they are seen in other granu-

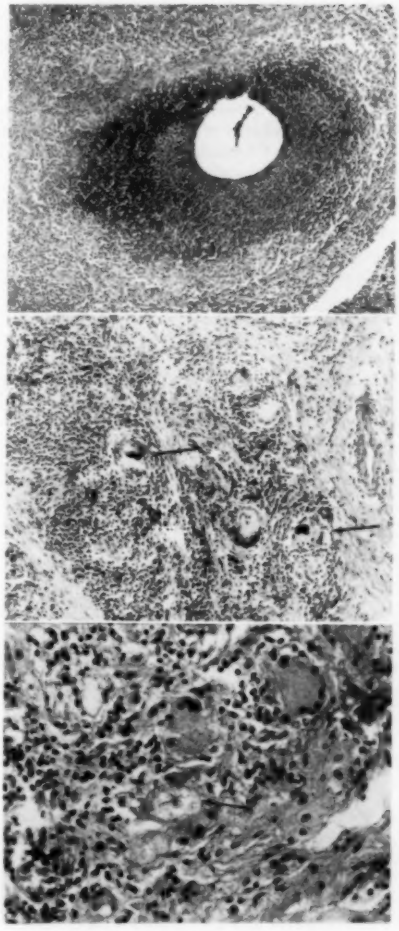

FIG. 31 (Top). In a typical chalazion the inflammatory reaction is centered about a droplet of fat liberated from the Meibomian gland. (AFIP accession 732397, × 115)

FIG. 32 (Center). Several multinucleated giant cells in this chalazion contain Schaumann bodies (arrows). (AFIP accession 780091, × 145)

FIG. 33 (Bottom). Asteroid body (arrow) in chalazion. (AFIP accession 692858, × 395)

lomatous lesions, as I have just shown you in chalazia.

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EXPERIMENTAL SARCOID REACTIONS IN HUMAN SKIN[1, 2]

WALTER B. SHELLEY AND HARRY J. HURLEY, JR.

I am here to tell you something about the experimental observations that we have made over the past five years (1–5) in studying the nature of the sarcoid reaction. We believe that the skin, just as it is a window to internal pathology, also may be an experimental substratum, an experimental area, so to speak, in which fundamental pathologic mechanisms can be discerned which go on in disease anywhere in the body.

When we started out, we were not primarily interested in sarcoidosis but, rather, in the axilla of man. In 1956 a patient presented a problem which was appearing for the first time on the dermatologic horizon. This was the deodorant granuloma. It was usually found in women who used zirconium deodorant sticks in the axilla. It was found bilaterally and appeared as fleshy and chronic papular lesions. On biopsy, it showed the typical histologic pattern of sarcoid.

We were interested in determining the cause and what initiated this reaction. There were many theories suggested and one of them was, of course, that this was simply a manifestation of sarcoidosis. As our studies progressed over a period of years, we learned that this reaction pattern actually was an unusual form of allergy, i.e., a delayed hypersensitivity reaction to zirconium.

A high-powered view of the skin test in a patient in whom we had experimentally produced this deodorant granuloma showed a skin reaction with all of the characteristics of cutaneous sarcoidosis. This sarcoid lesion was produced by the intradermal injection of a soluble pure zirconium salt in an extremely high dilution. The lesion was a pure epithelioidal cell response and one that persisted for many months.

As the study proceeded, we learned the following facts about the deodorant granuloma or the zirconium hypersensitivity reaction:

(*1*) The process is unique. It occurs only in persons who have become hypersensitive to zirconium. It does not occur in normal persons or in the individual who has not yet become sensitized. It is actually a rare reaction.

(*2*) The reaction is acquired. In other words, persons who were studied before they acquired this sensitivity had no abnormal reaction to zirconium. Apparently, there was no inborn error of metabolism in the way they handled the zirconium. It was a change, an altered reaction, if you will.

(*3*) The reaction persists. These subjects who were studied over a period of years did not change in their reaction to this skin test. They could be tested at repeated intervals and it was found that, when they repeatedly were given zirconium in the intradermal skin test, they always reacted with this local granulomatous formation. This was not limited to the true skin only; the same reaction could be produced as well in the subcutaneous tissues. It also will develop in any skin area, not being limited to the axilla.

(*4*) The nature of the reaction appears to be allergic. Of greatest importance is the fact that only extremely small quantities of the zirconium salt were required to produce results, which points up the allergic nature of this reaction. The necessary quantity was of the order of magnitude of a microgram, or a dilution of 1:100,000. For a histologic lesion, a reaction could be produced with a dilution of one per million. To answer one of our main problems, i.e., the question of how this material got into the skin, it was observed that there were actual breaks, minor abrasions in the skin from shaving, and it was through these little breaks in the epidermis that trace amounts of zirconium entered the skin of these sensitized subjects and produced this chronic reaction. The subjects remained in this hypersensitive state. One patient did not use the deodorant for a period of a year and then resumed it some months after the granuloma in the axilla had disappeared, whereupon she had a recurrence of the granuloma. It is, therefore, not a transitory state. The patients remain sensitized.

(*5*) The reaction is specific. Although the zirconium salt could be changed, the element zirconium had to be present to obtain this type of reaction. The reaction was specific for the zirconium ion; if we used beryllium, silica, or other chemical elements, no granulomatous reaction occurred.

I would like to compare this zirconium reaction with the Kveim reaction. Both are tested intradermally, and it is important to note that both reactions take time to develop. No gross lesion was seen in the skin in the first ten days in these patients with zirconium sensitivity. Nothing

[1] From the Hospital of the University of Pennsylvania, Philadelphia 4, Pennsylvania.

[2] Supported in part by research grant (E-2445) from the Division of Research Grants, U. S. Public Health Service.

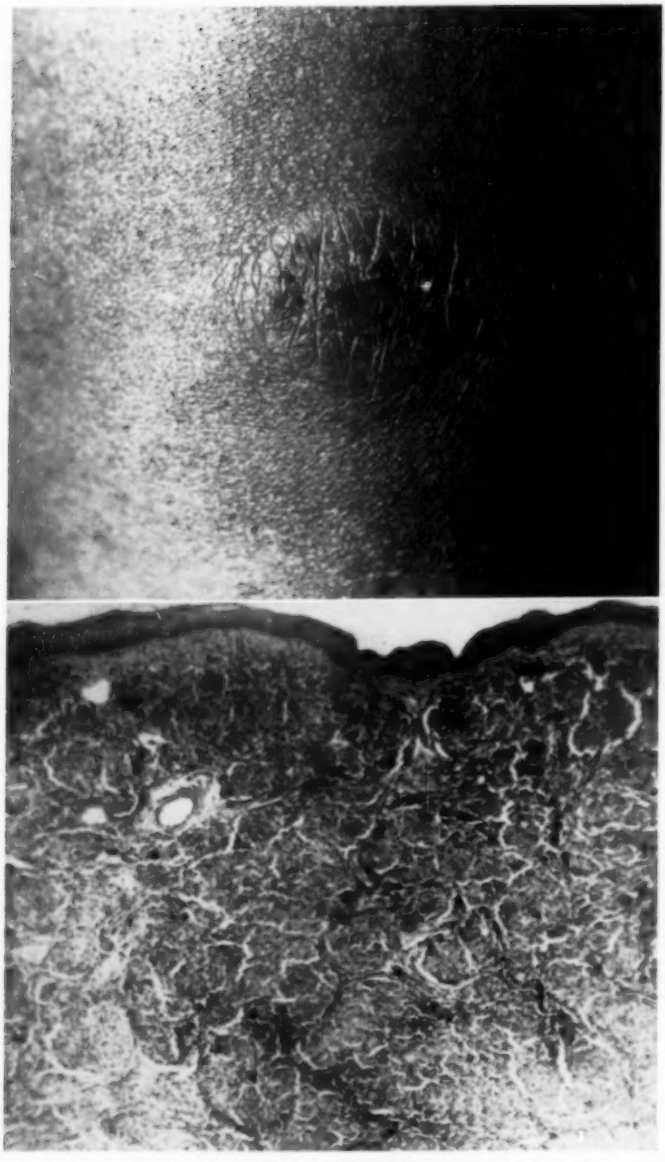

FIG. 34. Zirconium sarcoid papule. This photograph shows the delayed skin test reaction which occurred at the site of an intradermal skin test with sodium zirconium lactate. The skin test site remained normal for ten days. Following this, an enlarged papule developed which persisted for nearly a year. This skin reaction occurs only in the individual sensitized to zirconium. It mimics completely the positive Kveim reaction seen in sarcoidosis.

FIG. 35. Histologic sarcoid reaction found in papules shown in figure 34. This is a low-powered view of islands of epithelioid cells which were found on biopsy of the skin test reaction seen in figure 34. Histologically, this could not be distinguished from clinical sarcoidosis.

could be seen microscopically, and then round cells began to appear. After a period of weeks, the true epithelioid cell granuloma developed, as shown in figures 34 and 35. The longer one waited, the more obvious it became. As has been pointed out with the Kveim test, this is not a reaction which can be read within forty-eight hours after testing. It takes time (four to six weeks) for this slow delayed allergic reaction to take place fully.

The second half of our presentation leads into another experimental area. Not only do we see in our practice the zirconium hypersensitivity reactions following the use of deodorants in the axilla, but also a few patients who develop sarcoid reactions at the site of a tattoo.

The sarcoid reaction at the site of a tattoo is a specific reaction. (It is important to note that not all reactions encountered in tattoos are sarcoid.) The nature of the reaction can be ascertained by a biopsy. In one patient, the reaction was found to be sarcoid by histologic means. Since we had shown that patients may become sensitized to zirconium, with an unusual delayed reaction, it seemed advisable to take this patient and a number of other patients in the clinic and do exhaustive skin testing to all of the metallic elements that would be found in nature. The tattooed patient was thus tested with 71 different elements and showed no reaction to any of them. The test agent dilution was of the order of magnitude of 1:10,000. Concentrated solutions were not used. We also injected the available pigments which would duplicate those that probably had been used by the tattoo artist on this patient. Again, no reaction occurred.

In view of such results we realized that there might be another mechanism to account for the sarcoid granuloma that develops in these rare persons. In casting off several dozen hypotheses, we came upon the view that particle size might be a critical determinant.

Using colloidal silica as a skin-testing material, we found that we could regularly produce an epithelioid granuloma in all of our subjects. When we injected ordinary silicon dioxide, ground very fine, no epithelioid granuloma developed. However colloidal silica (particles of 25 to 30 mμ in size) injected in quantity routinely produced an epithelioid granuloma in every single subject.

Histologically, the skin following such an injection showed the presence of an epithelioid granuloma. After the tissue had undergone microincineration, the same area revealed residual silica. It seemed that the body handled colloidal silica by the simple mechanism of reticuloendothelial pickup.

In the light of these findings, it is our belief that in the patient with the tattoo, the pigment, over a period of years, reached a point where it was colloidalized by the individual. Only under certain circumstances and after a long period of time is there a weathering of the pigments so that they convert to this colloidal state. Once the colloidal dispersion has taken place, there is an immediate infiltration of reticuloendothelial cells which produces the rare tattoo granuloma.

There appears, therefore, to be a difference between the allergically induced sarcoid reaction occurring only in the sensitized individual and the colloidal reaction which we can obtain in everyone in whom an adequate amount of colloidal material is injected. The allergic reaction requires traces, whereas the colloidal reaction requires large amounts of material. It can readily be seen that a very small amount of colloidal material would be swept away in the lymphatics and no reaction would take place. It is only when the system is overloaded, locally, that the granuloma is produced.

Further, the allergic reaction requires specific material, such as zirconium, but the colloidal reaction does not depend upon a specific compound. Silica or silicon dioxide can be injected without producing a granuloma but, if injected in the colloidal state, this same substance will produce the granuloma. In fact, ordinary body soap (sodium stearate) will produce the same reaction if injected intradermally, but the body metabolizes these soaps at such a rate that the duration of the granuloma is short. The soap granuloma disappears in a month or so, whereas the silica granuloma remains in the tissue for seven and eight months.

To recapitulate, our experimental studies in

TABLE 8

SARCOID REACTIONS IN HUMAN SKIN

Allergic Type	*Colloidal Type*
Sensitized person	Everyone
Trace amounts	Gross amounts
Specific agent	Colloidal state
Examples	
Zirconium	Silica
Beryllium	Stearate
PPD	Palmitate

man have convinced us that the sarcoid reaction may arise either as a delayed type of allergic response or as a nonallergic reaction. In these responses, the histologic pattern is similar; yet the pathogenesis is remarkably different. The zirconium granuloma serves as a prototype of the allergic sarcoid response. This granuloma may be elicited experimentally by the intradermal introduction of extremely small amounts (0.02 γ) of a soluble zirconium salt. However, it can be elicited only in the rare individual who has acquired a hypersensitivity to zirconium. It does not develop in normal nonsensitized people. Nothing in the histologic pattern indicates the role or presence of zirconium. Finally, the experimental lesions show the typical maturation and subsidence noted in the Kveim reaction. We consider this zirconium granuloma to be an example of a delayed type of immune response which hitherto has received limited attention.

In contrast, the colloidal silica granuloma serves as a prototype of the nonallergic sarcoid response. Such a granuloma may be produced regularly in any subject by the intradermal injection of colloidal silica in comparatively large amounts (0.5 mg.). This granuloma in no way reflects an immune or hypersensitive state, but rather a local reticuloendothelial phagocytic response to a foreign material in the colloid state. Nevertheless, the clinical course and general histologic patterns mimic to a degree those of sarcoidosis as well as those of the allergic zirconium granuloma. Serial sections, special stains, or microincineration disclose the true foreign body nature of this reaction.

Our experimental studies suggest that sarcoidosis is best viewed as a reaction pattern, capable of being induced by numerous yet specific foreign substances (table 8). Some of these substances may act as allergens, others as foreign colloidal particles, but in each instance they give rise to the sarcoid reaction. Thus, we see sarcoidosis as etiologically analogous to dermatitis for, in both, the causes remain legion and may be either allergic or nonallergic. In both diseases, the study of individual patients may reveal individual causes. There is no single causal agent for either the sarcoid or the dermatitic reaction. Yet, further research may well disclose a common cause of sarcoidosis just as research many years ago disclosed that contact with poison ivy is a common cause of dermatitis. The search must continue, not for the cause of sarcoidosis but for the causes.

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SARCOIDOSIS IN CHILDREN

EDWIN L. KENDIG, JR.[1]

Apparently, pediatricians have not shared the increased interest in sarcoidosis which has occurred throughout the past few decades. In a review of world literature to February, 1953, McGovern and Merritt (1) found only 104 cases in children less than fifteen years of age. To these, they added 9 others, all diagnosed in hospitals in Washington, D. C. Undoubtedly, there are many unreported cases of recognized sarcoidosis in children, but it seems apparent that the disease is relatively rare in this age group.

Excluding 2 patients with doubtful diagnoses, only 6 proved cases of sarcoidosis in children less than fifteen years of age have been observed at the Medical College of Virginia Hospitals (2). Most noteworthy, however, is the fact that 3 cases occurred in siblings, a condition which, as far as we can determine, has not been reported elsewhere.

Since the 9 patients reported by McGovern and Merritt so closely parallel those noted at the Medical College of Virginia Hospitals, and since the number in each instance is small, they will be grouped together in the following discussion as the Washington-Richmond groups for comparison with those previously culled from the literature up to 1953 by the above-mentioned writers.

While study of the literature reveals that the youngest patient reported to have sarcoidosis, proved by biopsy, was a two-month-old male, most of the patients seen in childhood are in the older or adolescent age group. Of the 104 cases reported in the literature (table 9), 77 (74 per cent) were between the ages of nine and fifteen years. Of the Washington-Richmond series, 14 of the 15 patients were in this age group. Consideration should be given to the possibility that diagnosis may have been delayed because of the mild or insidious onset or the tendency of the disease toward regression.

Of the above 104 cases from the world literature, race was reported in 87, 63 of whom were white and 24, Negro. All cases in the Washington-Richmond groups were Negroes (table 10).

While only 2 of the 104 reported cases occurred in the same family, our group includes 3 siblings (table 11).

It is interesting, too, to compare clinical manifestations. Cummings and associates (3) noted involvement of the lung and/or hilar lymph nodes in 96 per cent of adult cases, while only 54 (52 per cent) of the 104 cases in children were so affected. The Washington-Richmond groups more closely resemble the adults reported by Cummings in that 14 of 15 cases showed such involvement (table 12). Peripheral lymphadenopathy was present in 32 of the 104 cases in the literature while 10 of 15 local cases presented such involvement. Skin lesions in children are relatively common (51 of 104 cases from the literature), and there was involvement in 8 of 15 local cases.

While eye lesions also occurred in 49 per cent of the group in the literature, practically all were minor ones. No case resulted in blindness. In contrast, 3 of the 7 cases noted in the Washington-Richmond series resulted in partial blindness.

None of the local group showed the syndrome of uveoparotid fever, while this occurred with relative frequency in the cases in the literature (27 per cent). On the other hand, bone involvement occurred with approximately the same frequency, with 30 of 104 cases and 4 of 15 cases, respectively.

Liver enlargement was noted in 5 and splenomegaly in 3 of the Washington-Richmond groups.

It may be seen, then, that our group of cases closely parallels that reported by McGovern and Merritt and differs considerably from that culled from the world literature (table 13). All cases in both the former groups were Negroes, and practically all were in the older age group. Hilar lymph node involvement was almost always present, the syndrome of uveoparotid fever did not occur, eye lesions were frequently present, and were of serious nature in 3 instances.

Diagnosis was corroborated in all of our patients and in 8 of the 9 cases reported by McGovern and Merritt by means of lymph node biopsy, and the tuberculin reaction was always negative (table 14).

Although McGovern and Merritt agree that there is usually "an absolute increase in serum

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TABLE 9

AGES OF PATIENTS IN WORLD LITERATURE AND IN WASHINGTON-RICHMOND GROUPS

World literature group	
9 to 15 years	77
Less than 9 years	27
Total	104
Washington	
9 to 15 years	8
Less than 9 years	1
Total	9
Richmond	
9 to 15 years	6
Less than 9 years	0
Total	6

TABLE 10

WHITE-NONWHITE DISTRIBUTION OF PATIENTS IN WORLD LITERATURE AND IN WASHINGTON-RICHMOND GROUP

World literature group	
White	63
Negro	24
Total	87
Washington	
White	0
Negro	9
Total	9
Richmond	
White	0
Negro	6
Total	6

TABLE 11

SIBLINGS IN WORLD LITERATURE AND IN WASHINGTON-RICHMOND GROUPS

	Cases	Siblings
World literature group	104	2
Washington	9	0
Richmond	6	3

globulin, so that the albumin-globulin ratio is frequently reversed," they make no detailed report of laboratory findings in their patients. Our group showed hyperglobulinemia in 5 of 6 cases (table 15). Both serum calcium elevation (more than 11 mg. per 100 ml. of serum) and alkaline phosphatase higher than 5 Bodansky units were present in only one of 4 tested cases.

Next to hyperglobulinemia, the most consistent laboratory finding was eosinophilia (more than 4 per cent). This occurred in 4 of 6 cases, and in 2 of these cases more than 7 per cent of eosinophilia was noted. Leukopenia, less than 5,000, was noted in 2 of the 6 cases. Elevation of the erythrocyte sedimentation rate was noted in 3 cases.

Finally, a suggestion as to the epidemiology of the disease should be noted. The 3 siblings less than fifteen years of age, mentioned earlier in the discussion, live in Nansemond County, Virginia.

TABLE 12

CLINICAL MANIFESTATIONS OF SARCOIDOSIS REPORTED IN WORLD LITERATURE AND IN WASHINGTON-RICHMOND GROUPS

Organs Affected	Reported World Cases	Washington Series McGovern and Merritt	Richmond Series
Peripheral lymphadenopathy	32	6	4
Lungs (parenchyma, hilar nodes)	54	8	6
Skin	51	6	2
Eyes	51	4	3
Bones	30	3	1
Uveoparotid fever	28	0	0
Liver	13	3	2
Spleen	24	1	2
Total	104	9	6

TABLE 13

SIMILARITIES OF WASHINGTON-RICHMOND GROUPS

All cases in Negroes
Practically all cases in preadolescent or adolescent ages
Hilar lymph node adenopathy almost always present
Eye lesions frequently present and often serious

TABLE 14

POSITIVE LYMPH NODE BIOPSIES IN WASHINGTON-RICHMOND GROUPS

Richmond series	6 (100%)
Washington series	8 (88%)

TABLE 15

LABORATORY STUDIES IN RICHMOND GROUP

	Cases Tested	Present
Hyperglobulinemia	6	5
Hypercalcemia	4	1
Elevated alkaline phosphatase	4	1
Eosinophilia	6	4
Leukopenia	6	2

One of the other 3 Richmond patients is also from Nansemond County and one from the adjoining county of Southampton. In this area, the chief crop is peanuts, and a large number of inhabitants work either in the peanut fields or peanut factories.

Investigation discloses that the Health Department of Nansemond County, which has a population of approximately 38,000, has on file about 50 subjects (practically all of whom are adults) in which a presumptive diagnosis of sarcoidosis has been made. Actually, in this county and the 2 adjoining counties of Southampton and Isle of Wight, there are more than 100 such subjects with suspicious roentgenograms.

It is true that pine trees grow in abundance in this same section, but the heavy concentration of presumptive cases in this small area would seem to indicate the presence of some other factor. Whether or not peanut dust plays a role is problematic. However, there is some information to the effect that the peanut growers have long been aware of some sort of chronic lung ailment which may develop among those working in peanut factories. Further, a great deal of this dust must be shaken from the vines when peanuts are harvested, and thus even those who are not factory workers may be exposed to the dust.

At the present time, a survey of sarcoidosis in this area is under way. Considerable help in the planning of this study has been given by Dr. Michael L. Furcolow of the United States Public Health Service. The first effort will be toward the establishment of unequivocal diagnoses in the suspected cases. From that it is hoped that a community survey and then an epidemiologic study will follow.

Summary

It must still be considered that sarcoidosis occurs with relative infrequency in children. Patients reported from the Washington-Richmond area differ from those found in the world literature in that all those in the former groups were Negroes; practically all showed hilar lymph node adenopathy, and eye lesions, often of serious nature, were frequently noted. It is suggested that peanut dust may in some way be implicated as the cause of sarcoidosis occurring in the Nansemond County area of Virginia.

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EXPERIMENTAL TREATMENT WITH CHLOROQUINE[1]

JAMES G. HIRSCH

Today I shall present evidence suggesting that chloroquine is an effective therapeutic agent for sarcoidosis. Before presenting this evidence, I think I might tell you how we came to administer chloroquine to sarcoid patients.

Several years ago it was noted that 15 to 20 per cent of serum specimens from our sarcoidosis service gave positive latex-fixation tests. This finding led us to speculate about the possible relationships between sarcoidosis and rheumatoid arthritis. One result of this speculation was the decision to give chloroquine to a few patients with sarcoidosis. Somewhat to our surprise, distinct improvement seemed to result from treatment with chloroquine.

The difficulty of assessing the results of therapy in a disease so prone to spontaneous remission as sarcoidosis need not be emphasized to this group. With this in mind, we have set up two separate clinical investigations of the effect of chloroquine in sarcoidosis. All subacute cases, that is, those of less than two years' duration, are included in a controlled "blind" study, the results of which will not be available for some time yet. Selected chronic cases of the type not likely to improve spontaneously have been given a six-month course of chloroquine, 250 mg. twice a day. The results of therapy in this chronic group form the basis for this presentation.

A summary of the results is shown in table 16. In all instances, the nature of the disease was confirmed by tissue biopsy and/or a positive Kveim test. Duration of disease ranged from three to eighteen years. Most of the patients presented skin lesions, and in each there was marked improvement or clearing of the dermal sarcoidosis following chloroquine therapy. Response of skin lesions was usually apparent after two to three months of treatment, maximal response often requiring six months or more. Characteristically, the lupoid skin papules were replaced by areas of increased pigmentation as they resorbed. Peripheral lymphadenopathy was present in only 3 patients; however, in each of these instances the nodes diminished markedly in size or disappeared following administration of chloroquine. Hilar and paratracheal nodes, in general, seemed to respond less dramatically. The influence of chloroquine on parenchymal pulmonary infiltrates was difficult to evaluate since, in many instances, the lung abnormalities in these chronic cases were of the fibrotic type. In 2 instances, there was distinct improvement of parenchymal pulmonary disease. Responses listed under "chemistries" reflect, for the most part, changes in sedimentation rate and in globulin fractions of the blood. These commonly returned to or toward normal following administration of chloroquine.

Patient *J.H.* in the table was of special interest, for she presented a chronic local sarcoid reaction of the lip without evidence of systemic sarcoidosis. Chloroquine brought about distinct improvement in this instance.

Of considerable interest is the fact that 3 of the patients with systemic sarcoidosis (*M.L.*, *D.W.*, and *E.M.*) experienced clinical relapse within three months following termination of chloroquine therapy. One of these patients responded satisfactorily to a second course of chloroquine without, thus far, ensuing relapse.

As a result of our experience to the present time, we are convinced that chloroquine has a beneficial effect on certain forms of chronic sarcoidosis, especially noticeable in patients with skin manifestations.

From a practical point of view, chloroquine may prove of great value in treating sarcoidosis. The only other agent available, adrenal steroids, is for the most part limited to use in particularly threatening situations, since most physicians are sensibly reluctant to employ a dangerous drug to treat a disease which is usually benign. Chloroquine has disturbing symptomatic toxicity in many patients, but is free from serious steroid hazards such as bleeding, tuberculosis, salt retention, et cetera.

Does the efficacy of chloroquine tell us anything of theoretic value in relation to the type of disease sarcoidosis represents? As most of you know, chloroquine was first introduced as an antimalarial. Many years later it was discovered, more or less by accident, to be reasonably effective for treatment of the so-called collagen disorders,

[1] From The Rockefeller Institute, New York 21, New York.

TABLE 16

SUMMARY OF RESPONSE TO CHLOROQUINE

Patient	Biopsy Proof		Duration of Disease	Response to Chloroquine Therapy				
	Tissue	Kveim		Skin	Peripheral Nodes	Thoracic Nodes	Lungs	Chemistries
			(*years*)					
M.L.	X	X	18	+		±	±	+
D.W.	X	X	11	+		+	+	+
M.T.		X	15	+		±		+
R.R.	X	X	4	+	+	0	0	±
L.M.	X	X	3		+	+	+	+
E.M.		X	6	+		0	0	0
M.B.	X	X	5	+	+	0	0	
J.H.	X		5	+				

\+ = marked improvement or clearing
0 = no improvement
± = slight improvement
Blank = not involved

rheumatoid arthritis and lupus erythematosus in particular. It is thus tempting to speculate that sarcoidosis, like the collagen diseases, is a chronic inflammatory state based upon hypersensitivity of some sort. Recent reports of the beneficial effects of chloroquine on granulomatous lipodystrophies and on infectious mononucleosis suggest, however, that this drug may exert an ameliorating action on chronic inflammatory reactions of various causes and types. It would thus seem more likely, at the moment, that chloroquine is a nonspecific therapeutic agent in much the same fashion as are adrenal steroids, and no conclusions seem warranted regarding significance of the response to chloroquine in terms of the pathogenesis of sarcoidosis.

Discussion

DR. HARDY: In patients with beryllium disease, we have only a few records of hypercalcemia, but many of hypercalciuria. It is possible that we do not have enough sequential serum calcium determinations to be certain of this point.

The number of cases with renal calculi in the beryllium series varies from 10 per cent of the 600 cases in the Beryllium Case Registry to as high as 20 per cent in small, well-studied series. We think the beryllium-calcium relationship may be a different pathologic disturbance from whatever is involved in stone formation in sarcoidosis. However, the diseases mimic each other so closely clinically that much, it seems to me, can be learned by well-designed parallel studies.

DR. HIRSCH: My only comment is in relation to the incidence of hypercalcemia and hypercalciuria. We, of course, have done serum calcium levels on all of our patients. Hypercalcemia, more than 11 mg. per cent, is a relatively rare occurrence.

Dr. Rich at the Rockefeller Institute did run a pilot study on about 30 patients, taken in series, and studied their urinary calcium. We were surprised to find that more than half of these patients showed hypercalciuria. These could be considered "run of the mill" patients, people who had no obvious trouble from disturbed calcium metabolism. Even though the numbers are small, we would suspect from our experience that hypercalciuria is common in sarcoidosis.

DR. JAMES: That is also our experience. We found hypercalcemia in 15 per cent of about 200 estimations. Hypercalciuria was present in half of a group of 24 patients in which it was sought by 24-hour urine determinations.

From the floor: I would like to ask whether the comment of Dr. Hirsch refers to the survey cases or to those in the hospital.

DR. HIRSCH: The survey series.

DR. SILTZBACH: May I elaborate somewhat on the hypercalcemia and hypercalciuria? We have seen hypercalcemia more commonly in the chronic stages of sarcoidosis than in the early hilar node phase although, in one instance of the latter, the illness was ushered in by symptoms ascribable to hypercalcemia. In our series of some 250 cases of sarcoidosis at Mount Sinai Hospital about 20 per cent of the patients had serum calcium levels of 11.5 mg. per cent or higher at some time during the illness. Hypercalciuria was even more common than hypercalcemia. Nine patients in this series developed renal damage serious enough to produce azotemia. Parenthetically, I might add that 8 of these 9 patients also had enlarged spleens, an evidence of chronic sarcoidosis. The renal damage reverted spontaneously in 6 of the 9 patients who had had azotemia, although it required an interval of two weeks to four years before a relatively normal renal status was achieved. Steroid therapy relieved the hypercalcemia in 3 patients, with improvement of the renal status, but these agents had to be continued in one patient for sustained control. One of our untreated patients with irreversible renal damage from hypercalcemia died of uremia.

DR. DUNNER: I might mention that in the Veterans Administration, with the chronic type of patient that we usually see, 35 per cent of 113 patients tested, a little higher figure than given here showed hypercalcemia, 11 mg. per cent or more. Coupled with this, Dr. Cummings had a survey made on the incidence or prevalence of renal calculi among veteran patients, and it is

interesting to a group discussing sarcoidosis that the highest areas of prevalence were in the southeast, particularly the Georgia area, and Atlanta specifically. Whether this factor is affecting our figures or not, I do not know.

DR. JAMES: Do you have any figures for hypercalciuria, Dr. Dunner?

DR. DUNNER: We have no figures on that.

DR. UEHLINGER: In my experience, hypercalcemia is associated only with those forms of chronic sarcoidosis which demonstrate involvement of the hilar lymph nodes and the lungs. Inasmuch as interstitial plasma cell pneumonia may also show a transitory hypercalcemia, hypercalcemia is probably not related directly to sarcoidosis but to a disturbance in the gas exchange in the lung.

DR. BELL: We have seen no relationship between the severity of pulmonary disease and abnormal calcium metabolism in sarcoidosis.

DR. LÖFGREN: During the period in question, 1949–1954, we found the incidence of spontaneous hypercalcemia (11.5 mg. per cent or more) in the sarcoidosis material in Stockholm to be about 7 per cent, but our impression is that the incidence has been lower during the last few years. According to our experience, the complication occurs only in cases of the generalized type, and for that reason the incidence rate will depend to a great extent on the composition of the material. For scientific purposes we have treated some patients with calciferol, and sometimes a transient hypercalcemia has been provoked in this connection. During the calciferol studies, we followed simultaneously the blood content of calcium and uric acid. When there was a rise of the serum calcium level, regularly there was also a rise of the uric acid level. We have no explanation of this phenomenon.

Regarding the relationship between hypercalcemia and renal damage in sarcoidosis, we made a study comparing the function and the histopathology of the kidneys. Regularly, when hypercalcemia was present, we also found bad kidney function and histopathologic changes of the kidneys. On the other hand, when there was no hypercalcemia present, the renal function was normal and the biopsy specimens were normal.

DR. JAMES: You have shown, Dr. Bell, that calciferol therapy, so often recommended by dermatologists, is menacing. Dr. Carl Nelson, himself a dermatologist, put an end to this form of treatment by controlled studies which showed that it was valueless.

DR. NELSON: Mr. Moderator, I must disclaim most of these attributes, but certainly, in the light of the evidence that has been presented by Dr. Bell, one would think that exactly the thing *not* to do in sarcoidosis would be to administer large amounts of vitamin D_2 or calciferol. I have always maintained this, but I did not know quite why I was holding to that viewpoint. We in this country are not the only ones to have given calciferol. I think Dr. Löfgren and your own countrymen have done it. This is an international error.

About 10 per cent of our material at Columbia University, mainly patients with chronic disease, will show hypercalcemia. If the serum calcium is really elevated, I take it to be a firm indication for steroid therapy.

DR. JAMES: I have given loads of calciferol in my time. The only ones still giving it are, I think, dermatologists.

DR. ZIMMERMAN: We have heard that beryllosis has a similar defect. I wonder if any other granulomatous diseases, such as tuberculoid leprosy, have been studied for this?

DR. JAMES: The last time we tried to find the answer to that question, Dr. Michael was working on it.

DR. MICHAEL: One other group that has had experience in administering calciferol and comparable compounds is the orthopedic surgeons. Twenty years ago it was fashionable to give calciferol and similar compounds to promote healing of fractures. The striking thing was that within a matter of a week, serum calcium levels had risen quite rapidly, and nitrogen retention accompanied it. We do not see nitrogen retention so often in an individual, with the 12 or so mg. per cent level characteristic of sarcoidosis. Is this a function of the speed with which calcium rises or a fundamental difference between the disease and the iatrogenic hypercalcemia?

DR. BELL: Such orthopedic patients for the most part are immobilized and, as you know, immobilization itself may produce hypercalcemia, hypercalciuria, and renal stones. What you say regarding the rapidity of onset of the blood urea nitrogen elevation may be true, but I know of no data on which to base any conclusions.

DR. JAMES: Do you subscribe to the theory that the more that goes out, the more is absorbed?

DR. BELL: No, we do not. Were the syndrome to develop because of primary renal calcium loss, the patients should develop osteomalacia just as do patients with renal tubulous acidosis, for example. To my knowledge this type of metabolic bone disease has not been described in patients with sarcoidosis.

DR. JAMES: We shall now discuss the presentation of Dr. Maumenee and Dr. Zimmerman. We see ocular involvement in about one-third or one-quarter of all patients with sarcoidosis; but, on the contrary, sarcoidosis is responsible for only about 5 per cent of cases of uveitis seen in the Uveitis Clinic of the Institute of Ophthalmology,

London. I take it that roughly the same figures hold in the United States.

DR. MAUMENEE: Yes, I certainly agree that that is a general figure; but, when we were interested in sarcoidosis at the Wilmer Clinic about ten years ago, we found that, if every patient who had uveitis had a routine biopsy of a lymph node, our incidence of sarcoidosis went up to 10 per cent. However, in the last study that we made in 1960, when we were not making routine biopsies, the incidence dropped to 3 per cent.

DR. JAMES: That is all cases of uveitis?

DR. MAUMENEE: That is right. I, therefore, think it is very important to know the interest of the investigator. Also, in your studies of sarcoid patients, the number of ocular involvements probably depends upon the interest of the ophthalmologists working with you.

DR. DUNNER: I think we are all interested in the eye as a possible portal of entry for the causative agent in those cases of involvement of the eye primarily rather than secondarily. I wonder if Dr. Maumenee has any thoughts as to what type of offending agents may be considered.

DR. MAUMENEE: No, I have not, and I think to even assume that the eye is a portal of entry, there would have to be lachrymal gland involvement. I would doubt very seriously if a patient who started out with uveitis could be used as an example of the eye as a portal of entry, because we have many other infections of the cornea and conjunctiva, in which there is very rarely a uveitis. Very few viruses that cause an external infection also cause an uveal involvement. I think most of the studies have referred to a higher incidence of uveitis, really, and not these relatively rare things.

From the floor: What is the incidence of unilateral uveitis?

DR. MAUMENEE: I am afraid I would have to go back and look at the series to really state whether they were all bilateral or whether there was any appreciable number of unilateral cases. We certainly see patients with more involvement in one eye than in the other. However, it is my impression at the present time that the majority of patients have had bilateral involvement. I think one of the most interesting things is the frequent involvement of the anterior segment as opposed to the posterior segment. This may be a clue. Perhaps there is some difference in the vascular nature of the iris that we do not yet know anything about.

DR. ZIMMERMAN: We have a number of very excellent examples of a granulomatous disease of the eye in which the lesions are always anterior, even more consistently so than in sarcoidosis, and that is leprosy. When leprosy involves the eye, it is always in the anterior segment. In comparing ocular leprosy with toxoplasmosis, diseases in which we know something about the causative agents, we have a pretty good explanation. *Toxoplasma gondii* likes nervous system tissues, and seems to infect the retina primarily; the uveitis, we believe, is secondary to the retinal infection. Leprosy bacilli, on the other hand, like cool tissues, and it is only in the late, massive dissemination that the internal viscera are involved. In using this clue for experimental work, Dr. Chapman Binford (1) has been able to produce lesions of leprosy in experimental animals by selecting inoculation sites where the body temperature is very low. So this is a convenient explanation. We know that the anterior segment of the eye has a lower temperature than the posterior segment. So, in these two diseases (toxoplasmosis and leprosy) something that seems to be characteristic of the metabolism of the infectious agent appears to explain its localization in the eye. Since we do not know yet that sarcoidosis is *not* an infectious disease, something peculiar to the nature of the etiologic agent may explain why it is almost always the anterior uvea that is most significantly affected in sarcoidosis.

DR. JAMES: Do you find ocular sarcoidosis uncommon in patients younger than eighteen?

DR. MAUMENEE: To give a specific answer, I would have to look at the age groups of these patients. We have not been impressed by any specific age group in these cases of uveitis. I do recall, at the moment, a child of five years who had a severe case, so it can occur—in rare instances, at least—in the very early age groups.

DR. CUMMINGS: In our experience with the veterans, we were impressed that involvement of the eye occurred about four times more frequently in the nonwhites than it did in the whites; and, in the nonwhite group, involvement of the eye occurred at an earlier age than it did in the white group.

DR. KENDIG: In a small group of 9 cases in children less than fifteen years of age reported from the Washington area, there were 4 cases of eye involvement, with one instance of blindness; of 6 cases from Richmond, 3 were cases of rather severe partial blindness. All patients were Negroes.

DR. SMITH: Preliminary to this meeting, we discussed sarcoidosis in children, and it seemed to be fairly rare in the North, but it is a common disease in pediatrics in North Carolina. In young children, it is observed particularly in the eye, but also in the lungs. They are mostly Negro children, so you have a racial factor. This not only raises a question of racial difference but also a question of sarcoidosis being a "place" disease. I think we have a place down in North Carolina

where it is a common disease, and it affects children in that environment, particularly Negroes.

DR. CHAPMAN: If I understood Dr. Zimmerman correctly, he stated that, in various sections of the eye, he was able to see lesions marked by inflammatory reaction. As far as I know, this is something peculiar to the eye so far as sarcoidosis is concerned. I do not think it is seen in sarcoidosis of the brain and meninges, or anywhere else where a sarcoid lesion involves some very sensitive membrane. I wondered if Dr. Zimmerman could elaborate on this point.

DR. ZIMMERMAN: Yes, I think it was very evident from the pictures that Dr. Uehlinger showed that this process of hyalinization is the same sort of phenomenon that we find here in the eye. The amount of productive material that would cause posterior synechias and devastating complications in the eye would pass unnoticed in the lung. However, I think it is fundamentally the same sort of process. The eosinophilic material, as Dr. Uehlinger pointed out, later goes on to complete hyalinization, and I think it is fundamentally the same sort of phenomenon as that which gives rise to an aqueous flare, synechias, a hazy vitreous, et cetera. I do not think it is safe to say that it does not occur elsewhere, although you may not see it. In the eye, leakage of exceedingly small amounts of protein from the capillaries can be detected because it clouds up the aqueous which can be viewed with the biomicroscope.

DR. SILTZBACH: I did not see any weeping of the pleura, but I did have a patient who was operated on for an open lung biopsy, and the pleura was found completely studded with small sarcoids which hung down like tiny grapes on a stalk. It simulated the picture of pleural tuberculosis in cattle. In spite of the fact that the entire pleura was covered with these exerescences, there was no pleural effusion. I do not know what the explanation for this is.

DR. DUNNER: Dr. Sones and I have discussed the rarity of pleurisy with effusion in sarcoidosis. I am reminded of a case that occurred in our hospital of a young woman with a negative tuberculin test and bilateral involvement of the lung. The question of sarcoidosis came up for discussion. In reviewing the past roentgenograms, there was one that showed pleural effusion, and the consultant decided that the patient had tuberculosis.

Recently, I received a written communication of a case of sarcoidosis in California, with bilateral pleural effusion. In our series of cases we have seen 2 cases. Dr. Sones told me that he also has seen 2 or 3 cases of sarcoidosis with pleural effusion.

DR. SMITH: There may be an anatomic factor involved. Dr. Hugh Burke of Montreal and his associates have been working on absorption of fluid from the pleura and have found that liters of fluid are absorbed daily. The little fluid that we see is simply the flowing fluid. So, there is an excellent mechanism for eliminating a considerable amount of fluid unless there is some blockage of the drainage system.

DR. JAMES: Dr. Maumenee, could you tell us very quickly about tuberculosis of the eye today? Do you ever see it?

DR. MAUMENEE: One more thing about the weeping of serum from the iris. A foreign body in the eye, an allergy to quinacrine hydrochloride, or surface irritants of a very mild nature will cause a diffusion of protein through the iris muscles. So I think, in addition to the fact that a small amount of fluid in the area might cause these lesions, the fact that the iris vessels do weep rather easily might explain why the eye shows these changes.

As far as tuberculosis of the eye is concerned, this is a subject that has been argued many times in ophthalmology. Dr. Zimmerman can answer this better than I, but the diagnosis of tuberculous uveitis in the past was made on a purely presumptive basis that the patient had tuberculosis elsewhere in his body, plus an histologic examination of the eyes. Unless the patient had a strong lesion in the eye which was not a real uveitis, but a massive inflammatory reaction that could be detected without difficulty, we have not been able to prove that these cases were due to tuberculosis, even though the patients had focal reactions in the eye to an injection of tuberculin. We have actually seen a focal reaction to tuberculin in the eye in a patient who had a retinal blastoma. So this is not a specific diagnostic point at all.

DR. JAMES: Discussion is now open on Dr. Shelley's, Dr. Kendig's, and Dr. Hirsch's papers.

DR. UNGAR: I would like to comment on Dr. Shelley's report. I think it is sometimes difficult to make a clear distinction between the allergic and the "colloidal" type of foreign body reaction. In a number of cases when bacterial vaccines are given, a certain proportion of children will respond with a foreign body reaction in the form of "antigen cysts." These cysts show a histologic picture not unlike that of a foreign body granuloma. I recall one case sent to me by a medical officer of health about three months after the injection of a prophylactic containing 5 mg. of aluminum phosphate. His query was, "Is it a tuberculous lesion"? It was obvious to me that the reaction was due to the injection of the vaccine. My own view is that certain persons will respond with marked local reactions to the injection of either an oily material or a mineral suspension.

I would like to refer also to some reactions we have noticed in those inoculated with tuberculin. Recently, I have seen a few cases in which, after

injection of a tuberculin in oily water phase (depot tuberculin), a nodule has been produced that, to the embarrassment of the tester, took a considerable time to resolve.

DR. SILTZBACH: I would like to ask Dr. Shelley a question. In the group that you presented in a previous paper in which you injected salts of seventy-one elements intracutaneously, you tested many sarcoidosis patients and never obtained a positive result at the injection site. In other words, unless a patient had beryllium disease, he would not react to the skin test performed with beryllium, and so on. When you did your work with colloidal silicon which you have just reported, did you also test sarcoid and nonsarcoid subjects? You said everybody reacted. Did that include sarcoid patients as well?

DR. SHELLEY: Yes, that did. We tested a few sarcoid patients, but did not find any remarkable differences.

DR. CHAPMAN: I want to ask Dr. Shelley a question. How long did the sarcoid-like nodule persist which he elicited with zirconium? Did it last several months, a year, or longer?

DR. SHELLEY: The skin test sites remained grossly evident for eight to twelve months. In the patients, the clinical lesions themselves remained as long as two to three years. Apparently, the duration is determined by how long it takes the body to metabolize or to eliminate a given amount of this element.

DR. HARDY: I am very much interested in this report. Do you know that a lung lesion was produced with zirconium in experimental animals? I assume you did not get any other organ involvement from the studies that you made with zirconium. Is that right?

DR. SHELLEY: That is right.

DR. HARDY: In England, Davies and Harding produced lung lesions with zirconium by inhalation experiments with small animals. You are telling us, are you not, that this is purely a local phenomenon. Experimentally, beryllium implanted in skin produces an indolent or subcutaneous granuloma without systemic disease.

DR. SILTZBACH: At the London Sarcoidosis Symposium in 1958, I believe that one investigator presented work in which skin tests were performed on patients exhibiting zirconium sensitivity using a zirconium salt as a test material. It is my recollection that he never produced any lung lesions in patients who reacted locally (in the skin) to the zirconium injection. In animals, I believe he could produce granuloma in the parenchyma by inhalation.

DR. HARDY: He really would not dare to give it to human volunteers by inhalation, would he?

DR. MAUMENEE: It was mentioned this morning that the serologic tests were negative. Were they negative for zirconium also?

DR. SHELLEY: We were unable to develop a serologic test for zirconium hypersensitivity. It proved to be an extremely difficult area of endeavor because this metal precipitates the proteins, including gamma globulin, in all serum. We were also never able to transfer this hypersensitivity state passively by means of leukocytes.

DR. UNGAR: I take this opportunity to ask if I could be enlightened on one phenomenon that might be relevant to the topic under discussion. I have learned now that sarcoidosis in the United States has a much higher percentage in Negroes. From the experience we have in East Africa, it seems that the Negro children vaccinated with BCG respond in much higher proportion and to a greater extent than the white or Indian population. The response of the Indian population is the lowest, about 70 per cent, and the white about 85 per cent; whereas the Negro local population responds about 99 per cent, and persistence of local reaction goes on much further. I would be interested in knowing what your experience is in Negroes as compared with whites.

DR. LONG: Dr. Aronson ran a great many tests with BCG at the Phipps Institute, and my impression is that in Negroes the injection nodule lasted much longer. Of course, that applies to many kinds of lesions in Negroes, not only of epidermal tissue, but many others—many, many others. So it is not at all surprising that this particular type of lesion, including sarcoid as well as the tuberculin, are somewhat more prominent in the Negro.

DR. CHAPMAN: I am familiar with some of the case reports from the world literature dealing with the very young who were reported to have sarcoidosis. The child who was two months old and who had so-called sarcoidosis almost surely had tuberculosis. It is not uncommon to find noncaseating tubercles in very young children, although one can perfectly readily cultivate the organisms from the lesions. So many of the cases that stand in the literature as very early sarcoidosis are suspect. On the contrary, the type of disease that Dr. Kendig has discussed is clearly sarcoidosis and it has, I think, from the standpoint of our speculation, rather considerable importance. It possibly points toward either an intrauterine transmission or perhaps an incubation period much shorter than some people have suggested.

We think, therefore, that there is no doubt about sarcoidosis occurring early in life. The only case in our area was a Negro boy, five years of age, who presented exactly the same kind of pattern which has been described and who clearly had sarcoidosis. It means, then, that we have to con-

sider whether some persons develop the disease as a result of a large dose of the agent, or if a certain age may perhaps allow the development of the lesion more rapidly, or if the supposed incubation period—and this should be in quotation marks—is very short.

From the floor: I have two questions with reference to the treatment with chloroquine. In those cases in which you achieved some remission, how long did you observe this effect to persist, and what was the change, if any, in the Kveim reaction?

Dr. Hirsch: Not sufficient time has elapsed to say how long it will persist. Of the approximately 6 patients whose six-month courses have been completed and who have been observed for a matter of three months or more after cessation, the disease of 2 patients did relapse, and one of these was given a second course to which he responded. The others have remained in a state of remission to date, but it is a very short time. The Kveim test has been repeated on a small number of these patients, and has really not been significantly different. It has remained positive, although the patients have gone into a state of remission. In a couple of instances, the second Kveim reaction was quantitatively less than the initial Kveim reaction had been, but we are not sure enough of our grounds to put any reliance on quantitative differences of this kind.

Dr. Israel: We have used chloroquine off and on since 1947, when Dr. Love of the Philadelphia Naval Hospital called to our attention the successful use of this drug in a critically ill patient. All other therapy had been ineffective and, because the patient had been in the near East, a trial of chloroquine was made. The patient made a dramatic recovery, and subsequently proved to have had sarcoidosis. We have used chloroquine occasionally since in patients who had symptoms for which use of adrenal steroids was undesirable. We have never seen another dramatic response, although some patients have felt better on this medication. Objective evidence of effectiveness has not been obtained.

Dr. Smith: I wonder if, in looking through the literature in connection with chloroquine, you have found a considerable series of sarcoids treated with potassium iodide.

Dr. Hirsch: No, we have not. We gave potassium iodide to 2 patients with sarcoidosis, precisely because we could not find in the literature that anyone had done it. So far as we could tell, nothing happened at all following the administration of potassium iodide.

REFERENCE

(1) Binford, C. H.: Histocytic granulomatous mycobacterial lesions produced in the golden hamster (Cricetus auratus) inoculated with human leprosy; negative results in experiments using other animals, Lab Invest, 1959, *8*, 901.

SUMMARY

Horace W. Bernton[1]

The sessions in this section have concerned themselves primarily with the clinical manifestations of sarcoidosis. There are many points of interest. Dr. Bell has made a significant observation in his study of the calcium defect in sarcoidosis. The fact that vitamin D levels were performed is important because the data indicate an endogenous rather than an exogenous intoxication with vitamin D. Dr. Bell also pointed out the clinical importance of measuring urine calcium. The importance of not relying simply on the serum concentrations of calcium to determine the presence of the calcium defect is clearly brought into focus. He points out the significance of low calcium and low vitamin D diet in the treatment of patients with the defect. Burr and associates have recently described patients with hyperparathyroidism and sarcoidosis. This too, of course, is an interesting combination of diseases. The cortisone test was found to be very helpful. In giving such a patient cortisone, it was possible to determine whether or not the defect could be reversed. In this particular case, the defect was not reversed by the administration of cortisone.

Attempts to chelate alimentary calcium, while theoretically possible, do lack practicability. However, to date, I know of no attempts to lower ingested vitamin D. I would be happy to be corrected. Since vitamin D is a fat soluble vitamin, one wonders if, with the administration of mineral oil, one could cause a relative hypovitaminosis D and replace the other fat soluble vitamins which may become deficient with such therapy.

Dr. Zimmerman suggested the need for studies of calcium metabolism in patients with other granulomas. I would like to echo this.

The presentation of sarcoid manifestations of the eye points out to us the importance of an examination by an ophthalmologist of patients with sarcoidosis. Many times there are external

[1] Sarcoid Clinic, Veterans Administration Hospital, Washington 7, D. C.

evidences of ocular sarcoidosis, but quite commonly there may be an early uveitis which the internist may not be able to detect. However, the ophthalmologist, with proper instruments, is able to detect it early. This stage of the disease is frequently successfully treated with topical steroids. The intraocular surgical scar shown us by Dr. Zimmerman was of great interest. It is reminiscent of such phenomena seen and reported elsewhere.

Dr. Kendig's comments are of interest because, to date, by virtue of Dr. Cummings' initiating studies on pine pollen, biochemists and physicians have learned much about the biochemistry of pine pollen and are learning more about its immunology. I wonder, if in the near future, we will find any factors common to pine pollen and peanuts. It is interesting that, as one studies the spectrum of the occurrence of acid-fast lipids in plant pollen, the pollen of gymnosperms appears to take the stain, but the pollen of angiosperms studied does not. Even the ginkgo, which is the transition between angiosperms and gymnosperms, is acid fast.

Regarding the intradermal injection of pine pollen antigens and subsequent biopsies, I would like to mention that, to date, no granulomas have been seen in either normal individuals or those with sarcoidosis.

THE NATURAL HISTORY OF SARCOIDOSIS

ANDREW C. DOUGLAS, *Moderator*

INTRODUCTION

DR. DOUGLAS: A study of the natural history of a disease is essential to provide guidance in clinical practice; but in a condition of undetermined causation, such as sarcoidosis, it may be further rewarding in that it may indicate new approaches to the problem of etiology. A description of the clinical features and course of a disease has, however, merit in itself. Addison, when describing the condition which bears his name, knew little of its etiology, but his description has stood the test of time. I am sure that much that we are to hear during this session regarding the natural history of sarcoidosis will also be of lasting value.

COURSE AND PROGNOSIS OF SARCOIDOSIS: PHILADELPHIA[1,2]

MAURICE SONES[3] AND HAROLD L. ISRAEL

INTRODUCTION

In the latter part of 1959, Dr. Harold L. Israel wrote to Dr. D. Geraint James and Dr. Sven Löfgren, hoping that we, as three groups, might set up a complementary study on the course and prognosis of sarcoidosis. Dr. Israel suggested that we might consider taking consecutive cases from 1949 to 1954, and compare certain factors, manifestations, and results obtained in the disease. These observations were to be presented at this session. Due to some confusion with the trans-Atlantic mails, these plans were not carried out as intended.

Dr. Löfgren studied the years 1949 to 1954, and Dr. James the years 1954 to 1958. Dr. Israel and I are presenting our series which ranges from the years 1947 to 1958. The experiences in London and Stockholm are included in the two papers which follow.

Some investigators (1, 2) have emphasized the benign course of sarcoidosis and its low mortality, while others (3, 4) have called attention to the frequency of disability and of death as a result of this disease. This variability of clinical experience may be due to many factors, among which are race, length of observation, selection of patients from hospital wards or from skin, eye, or pulmonary clinics, exposure to tuberculous infection and, finally, differences in definition of the disease.

The observations on the course of disease in 211 patients with sarcoidosis, which are presented herewith, are of interest for several reasons. Few reports of prolonged observation of large numbers of patients have appeared, and data are needed by which prognosis can be estimated and treatment evaluated. Comparison of the course of sarcoidosis in Europe, the United States, and other countries is important to ascertain whether sarcoidosis is a disease entity essentially similar in various parts of the world. Opinions still differ as to the frequency with which sarcoidosis and tuberculosis are associated. Finally, study of the natural history of this disease may provide clues to the nature of sarcoidosis.

CLINICAL MATERIAL

The 211 subjects included in this study comprise patients diagnosed between 1938 and 1958 as having sarcoidosis, and followed for at least three months at the Sarcoid Clinic of the Henry Phipps Institute, the Graduate Hospital of the University of Pennsylvania, and the Woman's Medical College of Pennsylvania. Clinical manifestations were absent or mild in many instances, while some patients were seriously ill with involvement of the lungs, eyes, kidneys, or heart. All patients had one or more biopsies which showed epithelioid cell granulomas consistent with sarcoidosis. Every effort was made by appropriate studies to exclude tuberculosis, fungal disease, and berylliosis. It is believed that the material is representative of sarcoidosis in a large American city, and is not weighted by unduly large numbers of patients with any one type of organ involvement.

The duration of observation was dated from the time objective evidence of sarcoidosis was first

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[2] Condensed from an article which first appeared in the *American Journal of Medicine*, 1960, *29*, 84.

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demonstrated, either by roentgenographic changes or by histologic evidence of epithelioid tubercles. The period of observation was terminated on May 31, 1958. After each examination the status was estimated on the basis of clinical manifestations and chest roentgenograms.

Of the 211 patients, 184 (87.2 per cent) were Negroes and 27 (12.8 per cent) were whites. Most patients were between twenty and forty years of age, and two-thirds were females (table 17). The mean age was 30.5 years for white patients and 27.3 years for Negro patients. More than 80 per cent of the Negro patients were born in the southeastern United States; however, a similar geographic origin was noted in tuberculous patients examined at the Henry Phipps Institute in Philadelphia (5). A history of household or other close contact with tuberculosis was elicited in 16.7 per cent.

Ninety-three patients received treatment with corticosteroid hormones during the course of their disease. The treated and untreated groups were analyzed separately, and the results revealed little difference (table 18). The more favorable results in the untreated group clearly reflect the practice of withholding treatment in asymptomatic cases. It is our opinion that, although corticosteroids definitely modify the clinical symptoms and pathologic changes, the ultimate outcome of the disease is not, as a rule, significantly altered by use of these agents. Similar observations have been made in asthma (6). Hence, it appears justifiable to group together treated and untreated cases in studying the course of sarcoidosis in our patients.

TABLE 17

AGE, RACE, AND SEX OF 211 PATIENTS WITH SARCOIDOSIS

Philadelphia, 1938–1958

Age	White		Negro	
	Male	Female	Male	Female
years				
Less than 10	0	0	2	1
10–19	2	0	6	11
20–29	6	5	36	71
30–39	6	4	11	33
40–49	0	2	2	8
50–59	0	1	0	3
60–69	0	1	0	0
Totals	14	13	57	127

OBSERVATIONS

Survival Rates

Despite the difficulty of tracing patients with relatively mild or benign illness, we were able to examine existing information or obtain data concerning a high percentage of patients (table 19). Twenty patients are known to have died during the period of observation. It is noteworthy that all were Negroes. No deaths occurred in the first year after diagnosis, but there were 4 in the second year. One death occurred in the third year, 3 in the fourth year, and 7 in the fifth year. Single deaths occurred in the eighth, tenth, thirteenth, nineteenth, and twentieth years after diagnosis.

Survival rates were calculated employing the life-table method in which it was assumed that the mortality among those patients lost to observation was the same as among those followed. This assumption may exaggerate slightly the mortality rates, since it is our belief that the patients lost to observation were often those who recovered promptly and saw no need for further medical care.

It is noteworthy that the survival rate of 88.8 per cent five years after diagnosis is considerably lower than the life expectancy (98.0 per cent) calculated for a normal population of this age, sex, and race. Similarly, the survival rate of 84.8 per cent ten years after diagnosis is further reduced from the expectancy of 95.2 per cent survival calculated for a normal population. Thus, sarcoidosis lowers life expectancy to a significant degree.

TABLE 18

STATUS OF 211 PATIENTS WITH SARCOIDOSIS AT END OF OBSERVATION PERIOD: COMPARISON OF 93 PATIENTS TREATED WITH CORTICOSTEROIDS AND 118 UNTREATED PATIENTS

Philadelphia, 1938–1958

Treatment	Cleared		Improved		Unchanged		Worsened		Died	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Corticosteroids	23	24.7	33	35.5	3	3.2	23	24.7	11	11.8
No steroids	50	42.4	34	28.8	14	11.8	11	9.3	9	7.6

TABLE 19

SURVIVAL RATE OF 211 PATIENTS WITH SARCOIDOSIS

Philadelphia, 1938–1958

Years	Number Alive	Number Dead*	Number Lost	Estimated Survivals	Survival Rate†	Survival Rate Normal Population‡
					per cent	*per cent*
0	211	—	—	—	—	—
1	197	0	14	211.0	100.0	99.6
2	171	4	22	206.2	97.7	—
3	151	1	19	204.8	97.1	98.8
4	123	3	25	199.9	94.7	—
5	104	7	12	187.3	88.8	98.0
6	85	0	19	187.3	88.8	—
7	70	0	15	187.3	88.8	—
8	56	1	13	184.0	87.2	—
9	42	0	14	184.0	87.2	—
10	35	1	6	178.9	84.8	95.2

* Three deaths occurred after the tenth year.

† Assumption is made that the death rates of those observed and those lost to observation is the same.

‡ Estimated for a population of similar age, sex, and race.

TABLE 20

OBSERVATIONS ON 211 PATIENTS WITH SARCOIDOSIS: CAUSE OF DEATH IN 20 CASES

Philadelphia, 1938–1958

Cause of Death	Necropsy	No Necropsy
Respiratory failure	3	6
Cor pulmonale	4	1
Myocardial sarcoidosis	1	—
Pulmonary hemorrhage	1	—
Pulmonary tuberculosis	1	2
Anthrax	1	—

TABLE 21

OBSERVATIONS ON 211 PATIENTS WITH SARCOIDOSIS: STATUS AT END OF OBSERVATION PERIOD

Philadelphia, 1938–1958

Condition at End of Observation	Patients		Mean Duration of Observation
	Number	Per Cent	
			years
Cleared	73	34.6	5.88
Improved	67	31.8	6.25
Unchanged	17	8.1	4.07
Worse	34	16.1	6.28
Died	20	9.5	5.96

Cause of death: Necropsy reports were available in 11 of the 20 patients known to have died (table 20). Designation of the probable cause of death in the other instances has been made on the basis of all available clinical and bacteriologic data. Diagnoses of tuberculosis have not been accepted in the absence of bacteriologic evidence. Three deaths were unquestionably due to tuberculosis, one to intercurrent infection with anthrax, and the remaining 16 were attributable to sarcoidosis. One patient died of myocardial sarcoidosis, 5 of cor pulmonale, 9 of respiratory failure, and one from pulmonary hemorrhage.

Status at End of the Observation Period

The interval of observation after diagnosis of the 211 patients ranged from three months to twenty years, with a mean of 5.9 years. Complete clearing was observed in 73 (34.6 per cent) of the group, and an additional 67 (31.8 per cent) were classified as improved (table 21). The disease remained unchanged in 17 patients, and grew worse in 34 (16.1 per cent). As noted above, 20 patients (9.5 per cent) died.

Infrequency of Recurrence in Sarcoidosis

Recurrence after complete clearing has occurred is extremely rare, and was observed in only 2 instances. In both patients, pregnancy may have been a factor.

Sarcoidosis and Tuberculosis

In addition to 3 fatal cases, 4 other patients developed tuberculosis which was confirmed by bacteriologic examination. In 5 additional patients, a diagnosis of tuberculosis was considered because tubercle bacilli were demonstrated by microscopy but not by culture or guinea pig inoculations, or because there was a single positive report among many negative sputum or gastric cultures. We have not regarded such patients as tuberculous.

Only one of the patients who developed tuberculosis had had corticosteroid therapy. This patient, who had extensive and severe pulmonary involvement due to sarcoidosis, was treated with adrenal steroids for twenty-one months, with considerable improvement. Three months after the steroid therapy was discontinued there was an acute onset of fever and cough which proved to be due to tuberculosis.

TABLE 22

RELATION OF INITIAL CHEST ROENTGENOGRAM TO COURSE OF DISEASE IN 211 PATIENTS WITH SARCOIDOSIS

Philadelphia, 1938–1958

Initial Chest Roentgenogram	Number of Patients	Cleared or Improved		Unchanged or Worse		Deaths	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
Negative	12	9	75.0	3	25.0	0	
Mediastinal adenopathy	71	46	64.8	21	29.6	4	5.6
Infiltration alone	56	34	60.7	15	26.8	7	12.5
Adenopathy and infiltration	72	51	70.8	12	16.7	9	12.5

Erythema Nodosum and Sarcoidosis

Erythema nodosum was recognized in only 6 (2.9 per cent) of our patients—2 white females and 4 Negro females. This is a frequency much lower than that observed in northern Europe, where erythema nodosum has been reported in a high proportion of Swedish patients (7) and in 31 per cent of English patients with sarcoidosis (8).

Relationship of Chest Roentgenographic Changes to Prognosis

The initial chest roentgenogram was normal in 12 patients (table 22). In 71 patients, mediastinal adenopathy alone was observed, and parenchymal infiltration alone was noted in 56 patients. In 72 patients, both mediastinal adenopathy and parenchymal infiltration were present.

The findings on the initial chest roentgenogram showed little correlation with the outcome at the end of the observation period (table 21). Whether they had adenopathy, infiltration, or both, two-thirds of the patients improved. Patients with mediastinal adenopathy alone had a mortality rate of 5.6 per cent, compared to 12.5 per cent for patients with parenchymal infiltration, but these differences are not significant.

Factors Affecting the Prognosis

As was noted, clearing or improvement occurred in 140 patients, and worsening or death in 54 patients. An attempt has been made to determine the influence of various factors on the outcome of the disease (table 23). It will be seen that the mean age and the sex distribution of both the patients who improved and those who worsened were essentially similar. A significant racial difference was demonstrable. The percentage of white patients among those who improved was 14.3 per cent, compared with 7.4 per cent among patients who worsened. Among the 50 Negro patients who had progressive disease there were 20 deaths, while among whites there were 4 patients who showed progression, with no deaths. The difference in mortality is not a significant one.

TABLE 23

A COMPARISON OF FACTORS WHICH MIGHT AFFECT PROGNOSIS IN 194* PATIENTS WITH SARCOIDOSIS

Philadelphia, 1938–1958

Factor	Improved (140, Mean Age 27.3 Years)	Worsened (54, Mean Age 28.8 Years)	Difference Significant at 0.05 Level
	per cent	*per cent*	
Sex (male)	36.4	33.4	No
Race: white	14.3	7.4	Yes
Negro	85.7	92.6	Yes
Three or more systems involved	25.0	75.0	Yes
Chest involvement alone	38.6	29.6	No
Liver or spleen	24.3	31.5	No
Skin	20.7	44.4	Yes
Eyes	16.4	20.4	No
Bones	12.1	24.1	Yes

* Seventeen patients whose disease was "unchanged" at the end of the observation period are omitted from this analysis.

As will be shown, the presence of cutaneous lesions appears to be a significant prognostic feature. It is noteworthy, therefore, that only 3, or 11.1 per cent, of white patients had cutaneous sarcoids, while 53, or 25.1 per cent, of Negro patients had dermal involvement. The less favorable outcome in Negroes has a better correlation with the greater frequency of skin lesions in this group than with the differences noted between other manifestations in the two races.

Among the patients who improved, 25.0 per cent showed involvement of three or more sys-

TABLE 24

MORTALITY RATES OBSERVED IN VARIOUS STUDIES OF PATIENTS WITH SARCOIDOSIS; RELATIONSHIP TO RACE AND TO OCCURRENCE OF CUTANEOUS AND OCULAR INVOLVEMENT

Place	Number of Patients	Negroes	Cutaneous Lesions	Ocular Lesions	Deaths		References
					Number	Per Cent	
		per cent	*per cent*	*per cent*			
London	200	—	16.5	25.0	11	5.5	James (10)
Boston	52	15.4	63.4	27.0	3	5.8	Longcope and Freiman (9)
London	102	—	16.7	16.7	7	6.9	Scadding (11)
Rochester, Minnesota	194	4.6	—	—	17	8.8	Carr and Gage (14)
Holland	150	—	6.7	18.0	14	9.0	Ten Have (15)
Philadelphia	211	87.2	26.5	17.6	20	9.5	Present report
Paris	41	—	9.8	31.7	6	14.6	Turiaf and Brun (16)
United States (Veterans)	540	—	—	—	84	15.0	Cummings *et al.* (17)
Philadelphia	97	77.7	46.4	—	15	15.5	Sones *et al.* (18)
Oslo	90	—	44.4	25.5	16	17.7	Nitter (4)
New York	35	85.7	40.0	20.0	7	20.0	Reisner (13)
Copenhagen	191	—	100.0	—	44	23.0	Gilg (12)
New York	52	79.0	25.0	29.0	13	25.0	Riley (3)
Baltimore	32	81.1	22.5	64.4	9	28.1	Longcope and Freiman (9)

tems while, among patients with progressive disease, 42.6 per cent had similarly disseminated involvement. Patients who had cutaneous and osseous involvement were significantly more often in the group with progressive disease, while no significant differences were demonstrable in relation to involvement of the liver, spleen, eyes, or chest.

Analysis by subgroups indicates that the differences observed according to race, and according to the number of organs or systems involved, are actually related to the occurrence of cutaneous involvement. The difference in prognosis between patients with and without osseous lesions appears to be the result of the difference in frequency of associated skin lesions. The difference in prognosis between patients with cutaneous sarcoids and those without cutaneous disease is the only consistently significant difference found in the homogeneous subgroups.

Thus, if all patients with skin involvement are analyzed separately, the differences in prognosis between whites and Negroes, between those with less than three and with three or more systems involved, and between those with and without osseous involvement, disappear. Similarly, if patients without skin involvement are analyzed, the differences in race and system involvement enumerated above disappear. The difference in prognosis between patients with and without cutaneous disease remains significant regardless of race and other system involvement.

DISCUSSION

Sarcoidosis as observed in Philadelphia over the past two decades is neither as benign as reports from Boston (1, 9) and London (10, 11) indicate, or as malignant as studies from Oslo (4), Copenhagen (12), and New York (3, 13) have shown. In table 24 some of the principal reports on the course of sarcoidosis are listed in order of increasing mortality rates. Whenever specified, data on the race of patients and the frequency of cutaneous and ocular involvement have been included. The extraordinary variation in death rates, ranging from zero to 28 per cent, is undoubtedly the result of many factors, such as length of observation, which influence the frequency with which complete clearing or a fatal outcome will become manifest.

Although the nature and pathogenesis of sarcoidosis remain enigmas, two observations deserve emphasis. The rarity with which fungal, tuberculous, or other bacterial complications follow the use of corticosteroid treatment of sarcoidosis is a powerful argument against an infectious causation of this disease. The infrequency with which recurrence was encountered indicates that, although sarcoidosis may represent a hypersensitivity reaction, it does not share

the relapse pattern so characteristic of collagen disease.

Summary

Observations are presented on the course of sarcoidosis in 211 patients, 184 Negroes and 27 whites, observed in Philadelphia for as long as twenty years, with a mean observation period of 5.9 years. Survival rates, calculated by the life-table method, were 88.8 per cent after five years of observation and 84.8 per cent after ten years of observation. Comparison with the life expectancy of normal persons similar in age, sex, and race indicates a considerable diminution of survival as the result of sarcoidosis.

Complete recovery was observed in 34.6 per cent, and improvement in 31.8 per cent, while in 16.1 per cent the disease worsened. The mortality rate was 9.5 per cent, with 16 deaths due to sarcoidosis, 3 to tuberculosis, and one to incidental disease. Four other patients developed tuberculosis, but only one of 93 patients treated with corticosteroids developed tuberculosis. In only 2 instances was recurrence of sarcoidosis observed.

The incidence of erythema nodosum was much less frequent than reported in English and Scandinavian studies, and clearing of mediastinal adenopathy occurred less often and less rapidly than in these two countries. With these exceptions, the course of sarcoidosis appears to be similar in Philadelphia and in northern Europe.

Although the prognosis appears to be less favorable in Negro patients and in those patients with many systems involved, analysis indicates that cutaneous involvement is the feature most closely associated with progressive and fatal sarcoidosis.

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COURSE AND PROGNOSIS OF SARCOIDOSIS: LONDON[1]

D. GERAINT JAMES

I have already outlined the thesis that the natural history of sarcoidosis varies with the type of disease. Subacute sarcoidosis is usually transient, self-limiting, and benign, whereas chronic sarcoidosis persists, sometimes progresses, and may terminate with unfortunate fibrotic sequelae.

Undoubtedly, the most predictable course and the best prognosis accompany erythema nodosum. This condition most commonly occurs during the spring season (figure 36) in young adult women of the reproductive years of life (figure 37). It is frequently observed among Irish girls living in London. Polyarthralgia usually precedes or accompanies the erythema nodosum, and fever is commonplace. A chest roentgenogram almost always reveals bilateral hilar lymphadenopathy, the Kveim test is positive, there may be depression of the Mantoux test and, because of abnormal serum globulins, the sedimentation rate is grossly elevated (table 25). It is safe to predict that the erythema nodosum, fever, and polyarthralgia will subside in a matter of three weeks (figure 38), and that the hilar lymphadenopathy will do so in the course of one year (figure 39). Recurrence and sequelae are rare.

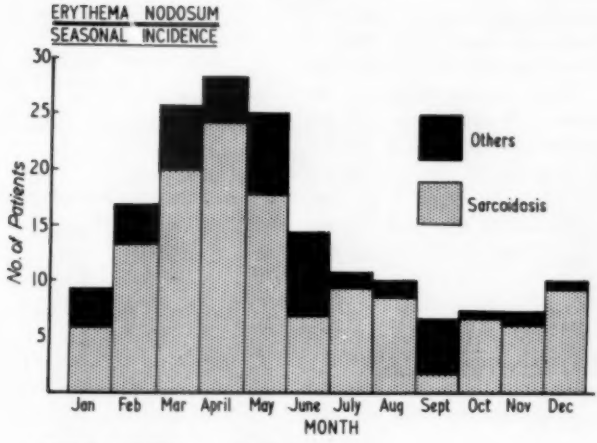
It is not possible, unfortunately, to define such a clear-cut natural history in other forms of sarcoidosis, except to predict that maculopapular eruptions, conjunctivitis, salivary-gland enlargement, Bell's palsy, and peripheral lymphadenopathy usually regress without treatment in the course of one year. On the other hand, chronic iridocyclitis, keratoconjunctivitis sicca, lupus pernio, plaques, and keloids persist unchanged or with minor fluctuations indefinitely.

In assessing the course and prognosis of a disease, it is essential to have an objective measure of assessment. As I have chosen the chest roentgenogram for purposes of this analysis, my remaining remarks will be concerned with the fate of pulmonary sarcoidosis and the influence of various factors upon it.

I have already indicated the benign outcome of the bilateral hilar lymphadenopathy associated with erythema nodosum; I shall now confine myself to the group without erythema nodosum. It is seen that resolution of the roentgenographic abnormality depends upon the stage of presentation of the abnormality. Spontaneous resolution can be anticipated in four-fifths of patients who present in the early stage of bilateral hilar lymphadenopathy, in three-fifths of those with hilar adenopathy and diffuse pulmonary mottling, and in only one-third of those with the late stage of diffuse pulmonary mottling (table 26). Resolution of all types of pulmonary sarcoidosis occurs in one-half of untreated patients within the first year of presentation; thereafter, year by year, spontaneous resolution can be expected in a few more until about 70 per cent of patients have shown clearing without treatment. It would appear that patients receiving corticosteroids are less likely to achieve resolution of the pulmonary abnormality (figure 40). However, it is important to emphasize the fact that the results are not based on a controlled clinical trial, and it would be fallacious to compare my treated and untreated patients or to draw any conclusions from such a superficial comparison. It can be seen, however, that resolution of pulmonary sarcoidosis occurs in about 45 per cent of patients receiving corticosteroids and that this figure remains about the same in succeeding years. In some instances I have withheld steroids and waited to see whether spontaneous improvement would occur; eventually, when it was not forthcoming, I have decided upon the use of corticosteroids. But, by this time, the pulmonary lesion had become chronic and persistent. This interpretation underlines our dilemma in choosing the optimal time for corticosteroid therapy. We do not wish to commence too early because of the high incidence of spontaneous improvement; on the other hand, we do not wish to withhold corticosteroids until a late stage of irreversible pulmonary fibrosis has made the position irremediable. Nowadays, I follow the course of pulmonary sarcoidosis for the first six months without treatment, and prescribe corticosteroids if the roentgenographic abnormality has progressed or deteriorated in that time.

I would like to draw attention to one final point concerning the question of the effectiveness

[1] From the Royal Northern Hospital, London, N. 7, England.



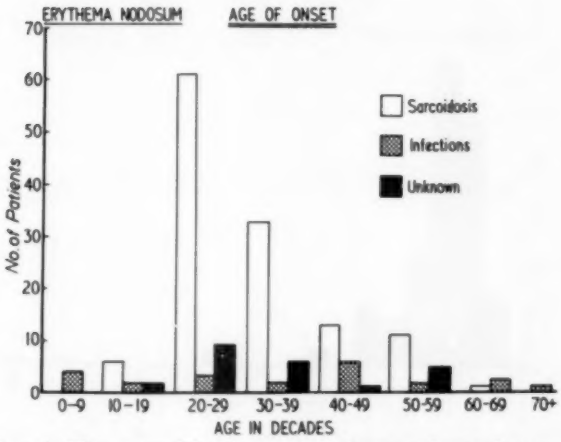


FIG. 36 (Upper). The seasonal incidence of erythema nodosum due to sarcoidosis and other conditions.

FIG. 37 (Lower). Age of onset of erythema nodosum due to sarcoidosis, various infections, and unknown causes.

of corticosteroids in pulmonary sarcoidosis. So far as I am aware, no controlled clinical trials have been conducted anywhere to guide us in their use. For this omission, we should stand with our heads bowed in shame, and endeavor together to rectify this state of affairs.

Let us now turn to other factors which may influence the prognosis of pulmonary sarcoidosis (figure 41). The age of the patient at onset of the disease is one factor. There was complete resolution of the pulmonary changes in 90 per cent of patients less than thirty years of age, but such resolution occurred in less than one-half of those older than thirty years.

The course of the pulmonary disease is more

TABLE 25

THE CLINICAL FEATURES OBSERVED IN 126 CASES OF ERYTHEMA NODOSUM

	Number	Per Cent
Bilateral hilar lymph nodes	116	91
Polyarthralgia	89	70
Females	93	74
Aged 20 to 29	62	49
30 to 39	33	26
Eye involvement	19	15
Other skin lesions	12	10
Negative Mantoux reaction 1:100	63	56
Positive Kveim test	107	94
Abnormal serum globulins	28	36
Raised serum calcium	8	13

protracted and the prognosis is worse if there is concomitant extrathoracic sarcoidosis. This is particularly so if there are skin lesions and bone cysts (figure 41). These lesions constitute the hallmark of chronicity in sarcoidosis and are associated with similarly chronic lung lesions. Roentgenographic clearing of the pulmonary abnormalities occurred in one-third of patients with bone cysts, in one-fifth with skin lesions, and in one-sixth of patients in whom bone and skin lesions coexisted.

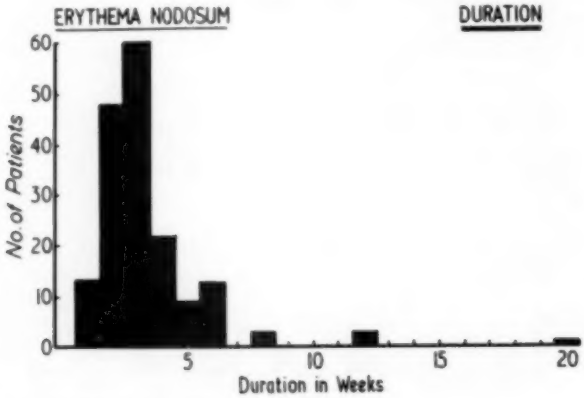
Let us summarize the problem from a slightly different standpoint, that of patients left with permanent pulmonary abnormalities (figure 42). The majority are seen to be those who presented at the late stage of pulmonary mottling, and who had associated eye or skin lesions, or sometimes both.

TABLE 26

SPONTANEOUS RESOLUTION OF PULMONARY SARCOIDOSIS IN PATIENTS WITHOUT ERYTHEMA NODOSUM

Initial Roentgenographic Abnormality	Number	Per Cent
Hilar adenopathy	83	80
Hilar adenopathy and mottling	65	60
Pulmonary mottling	71	30
Total	219	

In this series, there were 15 deaths attributable to sarcoidosis, 13 due to pulmonary hypertension with cardiac failure, and 2 due to nephrocalcino-



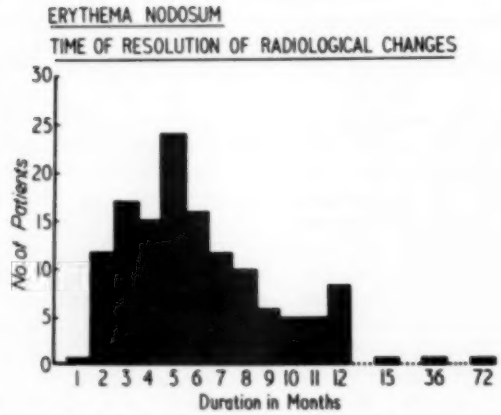


FIG. 38 (Upper). Duration in weeks of erythema nodosum due to sarcoidosis.

FIG. 39 (Lower). Duration in months of bilateral hilar lymphadenopathy associated with erythema nodosum due to sarcoidosis.

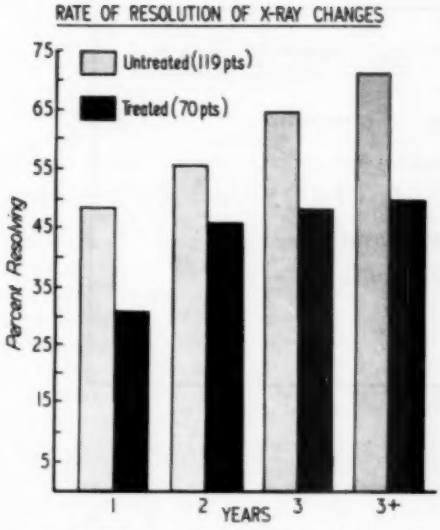


FIG. 40. Pulmonary sarcoidosis: rate of resolution of roentgenographic abnormality with and without oral corticosteroid therapy.

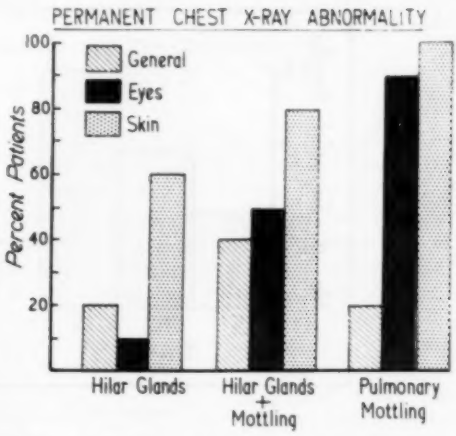


FIG. 42. Pulmonary sarcoidosis: the association of permanent roentgenographic abnormality with involvement of skin or eyes. The group termed "general" refers to patients without such involvement.

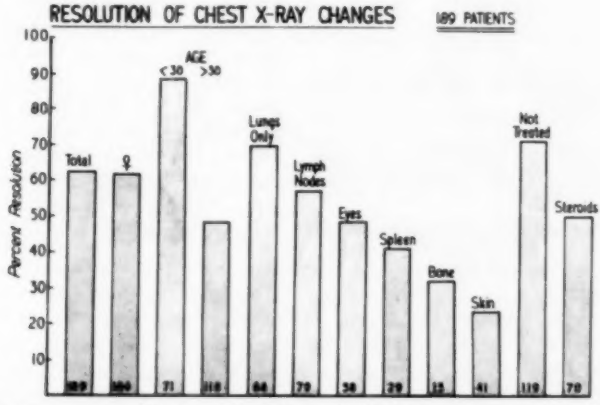


FIG. 41. Pulmonary sarcoidosis: percentage resolution of roentgenographic abnormalities related to sex, age, extrathoracic lesions, and corticosteroid therapy. The numbers at the base of each column are the totals for each group.

sis and uremia (figure 43). It is interesting to note that 12 of the 15 patients who died were women, who seem to be more prone to chronic skin lesions and, so, also to chronic pulmonary sarcoidosis.

Sarcoidosis would remain a relatively benign and unimportant disease but for the development of certain devastating complications, which are due to the development of irreversible fibrosis in the lungs and eyes, and to abnormal calcium metabolism affecting the kidneys (figure 44). In assessing the prognosis, it is important to assess the degree of functional failure of lungs, heart, eyes, and kidneys. In the practical management of sarcoidosis, it is the physician's duty to diagnose the condition sufficiently early so that the judicious use of corticosteroids may prevent these unfortunate sequelae. In fact, the main indications for corticosteroid therapy are directed toward this goal. Steroids should be prescribed when

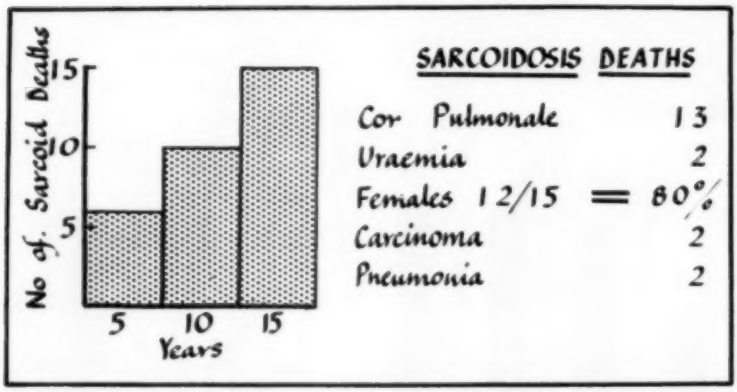


FIG. 43. Causes of death, and duration from initial presentation.

Complications of Sarcoidosis			Failure of
Pulmonary fibrosis	→	Cor pulmonale	Lungs Heart
Chronic uveitis	→	Glaucoma Cataract	Vision
Hypercalcemia Hypercalciuria	→	Nephrocalcinosis	Kidneys

FIG. 44. The complications causing functional failure in sarcoidosis.

there is ocular involvement, worsening or static pulmonary involvement, or persistent hypercalciuria.

In summary, the course and prognosis of sarcoidosis depend upon the type of disease. Subacute sarcoidosis tends to be transient, self-limiting, and benign, as is the case with erythema nodosum, maculopapular eruptions, conjunctivitis, salivary-gland involvement, Bell's palsy, and peripheral lymphadenopathy. Chronic sarcoidosis persists indefinitely, as is seen with chronic iridocyclitis, keratoconjunctivitis sicca, lupus pernio, plaques, and keloids. Factors influencing the course of pulmonary sarcoidosis include the type of intrathoracic lesion, the age at onset, and the presence of concurrent extrathoracic lesions. The prognosis is also based upon the degree of fibrosis supervening; the indications for corticosteroid therapy are mainly directed toward the prevention of these fibrotic sequelae.

COURSE AND PROGNOSIS OF SARCOIDOSIS: STOCKHOLM[1]

SVEN LÖFGREN AND SVEN STAVENOW

It was pointed out earlier in this Conference that the case materials from the United States, Great Britain, and Sweden are obviously different in their composition. On the whole, the Stockholm or Swedish material is composed to a very large extent of mild cases, in which the disease is detected through routine examination or because of the occurrence of erythema nodosum. These differences in the severity of the disease will explain why the incidence figures, the prognosis, and the final outcome of the cases may vary in the different countries.

In this presentation of the Stockholm material, we have followed the suggestion that all cases seen in the period 1949 to 1954 be discussed. All of the patients in this six-year series were admitted to St. Göran's Hospital. There were 132 patients, 60 (45 per cent) resulting from routine examination. In 22 patients (17 per cent) the disease was discovered because of respiratory symptoms, in 33 (25 per cent) because of erythema nodosum, and in 17 patients (13 per cent) for other reasons. In one instance sarcoidosis was observed in mother and daughter, and in another sarcoidosis was found in two sisters who were not twins.

With regard to age, no children are included in the Stockholm material. In fact, we have never seen a child with sarcoidosis, and there are relatively few cases in persons younger than twenty years. After age twenty, however, there is a sudden rise in incidence, the peak number of cases occurring between the ages of thirty and thirty-nine years. With regard to sex, 88 of the 132 cases were females and 44 were males, a ratio of 2 to 1.

As was explained in a previous paper, we regard pulmonary involvement as essential in the picture of sarcoidosis. For this reason, only patients with intrathoracic lesions are included in this series. The great majority, 118 patients (90 per cent), show hilar adenopathy, with or without pulmonary infiltration.

Skin sarcoids were found in 39 patients, or 32 per cent of all the cases—a rather high incidence. We would like to point out that cases of skin sarcoidosis seen in Stockholm are not similar to those seen in the United States. As a rule, the Stockholm cases show very small skin changes, often occurring in old scars. The phenomenon of sarcoidosis occurring in scars is most interesting. We have seen about 50 such patients with sarcoids in old post-traumatic or postoperative scars. Since the post-traumatic scars are often contracted in childhood, there may be an interval of twenty to thirty or forty years before the scar swelling takes place in connection with the development of pulmonary sarcoidosis. With postoperative scars, the interval between surgery and scar swelling, as a rule, is shorter.

In this series, we found 10 patients with spontaneous hypercalcemia connected with kidney involvement. In our experience hypercalcemia is always associated with a disturbance of renal function.

Roentgenograms of the bones were not done routinely, which makes it impossible to say anything regarding the incidence of this involvement. In our experience, bone involvement is a rare phenomenon in mild cases of sarcoidosis. In 2 of 8 generalized cases examined, the roentgenograms of the bone revealed changes typical of sarcoidosis.

Electrocardiograms were obtained in 39 cases, 2 of which showed signs of transient myocardial lesions.

Joint swellings have been observed in 43 patients (33 per cent), 3 males and 40 females; they are especially seen in connection with erythema nodosum.

In considering prognosis, the first question that arises concerns treatment. Treated and untreated patients were compared for prognosis. Comparisons were made after follow-up periods of one, two, and four years; at each time period a difference was found, namely, that the treated cases had the worst prognosis. This is apparently due to the same reason given by Dr. James, that we are very restrictive with therapy. Similar comparisons were made for females alone, and again the treated patients showed a worse prognosis than the untreated. It is important,

[1] From St. Göran's Hospital, Stockholm, Sweden.

therefore, not to exclude the treated patients in formulating ideas for prognosis.

When the total material was separated into males and females, we found that the prognosis was worse for the males at each period of observation. In other words, prognosis was consistently worse for males than for females, regardless of treatment. The question then arose: Could this difference between males and females be due to the fact that erythema nodosum is more common among the female patients? (In this series, 3 males and 30 females had reacted with erythema nodosum.) To answer this question, we compared the prognosis in females with and without erythema nodosum. It could then be shown that the erythema nodosum group had a better prognosis. However, when we excluded the erythema nodosum cases from both the males and the females, the prognosis still remained worse for the males.

When we compared cases in which three or more systems were involved, we found in the total material a definite difference in that the prognosis with regard to pulmonary lesions became worse as the number of systems involved increased. So far as any single system was concerned, kidney involvement was associated with the worse prognosis.

When comparing two age groups, those older than and those younger than the mean age, we found, as in the English material, that the females in the younger age group showed a better prognosis than those in the older group.

No difference in prognosis was observed between patients with and without skin lesions. However, as was stated previously, the Stockholm series of cases showed many very small sarcoids, while those in the United States consisted of severe cases that showed extensive skin sarcoidosis.

Discussion

Dr. Douglas: These papers are now open for discussion. Perhaps I may start by asking Dr. James about polyarthralgia. Do you think this is a manifestation of sarcoidosis or simply part of the erythema nodosum picture?

Dr. James: It is sufficiently common to be regarded as part of the picture, possibly due to some hypersensitivity mechanism.

Dr. Douglas: Have you seen a joint effusion?

Dr. James: It is comparatively rare.

Dr. Douglas: We thought we saw one in our series, too.

Dr. Siltzbach: We have heard that the eventual outcome of the illness in patients treated with steroid therapy does not differ materially from that of the untreated group. Yet, paradoxically, all of us continue to use steroids in treating a fair proportion of our patients. Why? From what I have heard here today, it seems to me that none of us would withhold steroid therapy from patients with significant ocular lesions, with central nervous system and myocardial involvement, or with persistent hypercalcemia and renal damage. We prescribe steroids even though it cannot yet be shown that the sum total of survivors is increased by their use, or that the number of disabled individuals is sharply cut.

I would like to stress a point which has already been made clear by the speakers. The steroid-treated group contains a higher proportion of patients with severe disease processes than the untreated group. One would anticipate a poorer outcome in them. It seems to me that none of us would question the fact that a patient in whom ocular sarcoidosis, for example, is recognized early and is treated with steroids has a better chance of keeping his sight than a patient whose lesions are left untreated.

Steroid therapy at the present time has an important place in the treatment of sarcoidosis and, in my experience with almost 100 patients with sarcoidosis treated by this means, this therapy is applicable in about one-third of the cases which we encounter.

Dr. Hardy: I agree with Dr. Siltzbach and urge, because of the bad prognosis in beryllium disease, that treatment be continued, risking possible side effects. We now have a good series of patients who have been under therapy for as long as ten years, in some cases with earlier corticotropin, and then a steroid preparation. I believe that once there is an abnormality which can be measured, such as a large spleen or an increase in the serum protein, patients with beryllium poisoning should be treated promptly and over a long period of time. The discussions today have indicated that the steroids make an impression on the pathologic changes associated with sarcoidosis, and the same is true for beryllium intoxication.

Dr. Michael: We are in agreement about the use of steroids in eye disease, hypercalcemia, and myocardial disease. The group that should concern us now is that which results in pulmonary fibrosis. How can we pick out these patients when their disease starts and, by the use of steroids, prevent fibrosis? I would urge the organization of such a study.

Dr. Nelson: Since Dr. James and Dr. Sones have both found it to have such a gloomy prognostic import, are we to assume, and are they prepared to say, that extensive cutaneous sarcoidosis

is to be added to our list of definite indications for steroid therapy? Would they go so far as to say that? Does the presence of cutaneous lesions help us to pick out some of the cases that Dr. Michael just mentioned?

DR. SONES: I would say yes, especially if one finds, in addition to extensive cutaneous involvement, pulmonary involvement or a large liver. Such patients should be treated with prolonged steroid therapy. We have had patients under continuous corticosteroid therapy for as long as five years.

Our statistics for treated and untreated cases appear to show no difference. When we select for treatment those patients who have extensive and progressive disease, no matter how long we treat them or how many courses of corticosteroids we give they are eventually going to die of their disease. However, we probably prolong life. We agree with Dr. Siltzbach and Dr. Hardy that we will treat every patient with ocular involvement, with extensive progressive pulmonary involvement, and with myocardial involvement.

I think that the "acute" stage of sarcoidosis, often seen in England and Sweden, will usually clear without treatment. We have not seen many of these cases. As a matter of fact, our series of patients with adenopathy alone do not show the same course that Dr. James's and Dr. Löfgren's cases have shown. Many of ours take a longer time to clear up, and many progress to extensive pulmonary involvement.

DR. CUMMINGS: I am reminded of pertinent remarks made during the morning that perhaps will help explain the paradox of the favorable follow-up observed by Dr. Löfgren in a series of asymptomatic cases detected by chest roentgenograms, and the follow-up studies which have been recorded in groups which, I suspect, represent principally the symptomatic, long-term patient. To speak to this point for a moment, our five-year follow-up of 540 patients of the latter type, namely, the individuals who came to a veterans hospital because of some symptom, indicates that the mortality rate is in the order of 3 per cent per year, which I think is of some significance.

But perhaps even more pertinent than the statistics, per se, is the fact that a follow-up study is only as good as the autopsy review. In our own experience, we were quite stunned to learn that patients diagnosed as having sarcoidosis with repeated "biopsy confirmation" often were found, at autopsy, to have no evidence of sarcoidosis or to have granulomas of specific etiology. I suppose I am too proud to admit that our diagnostic acumen is not too different from others. Therefore, I would like to propose that we encourage sustained follow-up studies in various parts of the world, with emphasis on obtaining autopsy review, if possible. This, I think, is a question that could be dealt with by one of the sections later in the Conference.

DR. DOUGLAS: With regard to skin involvement, I wonder if I might briefly show a set of slides. Disfiguring skin lesions can, I think, be an indication for treatment, even though they may not be associated with involvement of important organs. This slide shows marked lesions of lupus pernio on the face of a middle-aged woman in 1954. Four years later the lesions had worsened considerably. The patient was, by this time, miserable about her appearance and would not go out because of her unsightly nose. We thought this was well worth treating. She now has a nose of reasonable size. It is still somewhat discolored, but can be easily camouflaged with the use of cosmetics. I think disfiguring skin lesions of this type also constitute an indication for treatment with corticosteroids.

SUMMARY

EDWARD DUNNER

The members of the program committee should be congratulated for selecting three speakers who so capably presented such a large body of clinical material for our consideration.

Reports from the last meeting of the international group indicated differences of opinion and data in several areas. One of the most important was whether or not sarcoidosis is related to tuberculosis. The British view in favor of this relationship differs from that in the Scandinavian countries and the United States, where the weight of evidence is thought to be against a direct relationship. As for elevated serum calcium levels, they seem to occur more commonly in the United States and England than in Norway and Sweden. Erythema nodosum is less frequently reported in the United States than elsewhere. Despite these differences, the impression is gained from today's session that we are indeed speaking about the same disease, but with considerable variation in patient material.

I was particularly impressed with the slide shown by Dr. James in which there was an implication of a seasonal incidence of sarcoidosis from March to May. If this coincides with the pine pollinating season in England, I believe this would give much joy and comfort to Dr. Cummings.

Dr. James also mentioned a figure of 7 per cent

of patients with erythema nodosum and a high number of patients with polyarthralgia. The latter reminds me that in our review of veterans' records we noted the occurrence of arthralgia early in the course of the disease, and I must confess that we ruled several of these patients out of our study as having arthritis, rheumatic fever, et cetera. However, the occurrence of erythema nodosum definitely was a rare finding.

The suggestion for the need of a controlled study to evaluate steroid therapy in pulmonary sarcoidosis bears emphasis.

Dr. Douglas mentioned that 3 per cent of his patients had bone lesions, which is about the same figure reported in the Veterans Administration series, but much less than reports in the literature or by Dr. Sones.

Handicapped somewhat by not having the prepared papers available for review, I jotted down some questions last night just to see how much further along we might come toward answering them as a result of this session. I should like to pose them and comment upon them in light of what has transpired today.

(*1*) How much closer are we to learning about the incubation period? I enjoyed the picture that Dr. Shelley showed of the man with the tattoo. We had one such case of a tattooed veteran who seven years later developed nodules in this area, followed by axillary lymph node enlargement and pulmonary involvement. This led us to think that perhaps the incubation period should be thought of in terms of years rather than months. Dr. Shelley's explanation of the weathering and the transformation to colloidal material is plausible. Also, in Dr. Kendig's presentation on children I thought we might have a clue to the incubation period, since fewer false leads occur with children, as compared to adults who work in peanut factories and other such unusual environments. Similarly, I thought the presentations on eye involvement, since that might be a more acute manifestation, would give us a clue to the incubation period. The same is true of patients with erythema nodosum. I am intrigued by the colleens who come to London, marry, and develop erythema nodosum and sarcoidosis.

(*2*) What is the incidence or prevalence of sarcoidosis? Dr. Schonholzer, in his report pertaining to recruits in the Swiss Army, mentioned a figure of 14 per 100,000. Dr. Hirsch mentioned a survey of New York City Negroes which produced a figure of 10 per 10,000. Dr. James mentioned 3 to 5 per 10,000. In our World War II veterans' population, which is a more select group, we know that there is at least one per 100,000, and certainly many more.

(*3*) What is the portal of entry of the causative agent? I was impressed with the remark which I believe Dr. Löfgren made about scars and postoperative trauma. At one period in this study, I thought that these might be a clue, but that notion faded, as did many others. Is the causative agent ingested, inhaled, or what?

(*4*) Is there or is there not a relationship between sarcoidosis and tuberculosis? I believe we are tending more and more to get away from the assumption of a direct relationship.

(*5*) Is sarcoidosis a disease or a syndrome? This came under heavy discussion this morning.

(*6*) Can a common denominator as to animal, vegetable, or industrial contact be established or ruled out? We attempted in the VA Cooperative Study to do a study of this nature. Perhaps the questions we asked were wrong. At any rate, we could not come up with a common denominator.

(*7*) What are the early and late symptoms and signs of sarcoidosis? I think it is time, as Dr. James mentioned earlier, that we separate our cases into the early transient group and the chronic group, and not lump them all together. This could facilitate a better understanding of sarcoidosis.

(*8*) Is sarcoidosis as benign a disease as has frequently been reported, or does it represent a difference in clinical experience? Dr. Cummings mentioned our figures of 540 patients admitted to VA hospitals between the years of 1949 and 1951 with a diagnosis of sarcoidosis. Eighty-four, or 15 per cent, died within a five-year period. Autopsy was performed in 50 of these cases. He went on further to mention the differences in diagnoses. The most frequent cause of death was, as you would expect, cor pulmonale.

If I may return for one moment to item (*7*) above, the early and late symptoms and signs, not much mention was made of involvement of the heart. Peacock and others reported in the journal, *Circulation*, July, 1957, that the heart is involved in 20 per cent of the cases of sarcoidosis.

Also, until 1952, joint involvement in sarcoidosis received little or no attention in the literature. Since then, the incidence has been reported as 10 to 25 per cent. Arthralgia may be an early symptom.

(*9*) Can the specificity of the Kveim test, as a diagnostic test, be established? I will skip this because we will hear more about that as the program continues.

(*10*) What are the indications and contraindications for the administration of corticosteroids to patients with sarcoidosis? Briefly, the indications for the use of corticosteroids are: (*a*) involvement of a vital organ which may threaten life; (*b*) acute or subacute involvement of the eye; (*c*) progressive pulmonary involvement as manifested by in-

creasing symptoms, unfavorable changes in the chest, or deterioration of pulmonary function; (*d*) patients who have hypercalcemia or hypercalciuria; (*e*) patients who are acutely or subacutely ill, as evidenced by loss of weight, fever, et cetera; and (*f*) patients who have progressive and disfiguring lesions of the skin.

Those who probably should not be treated according to our present knowledge include: patients who have only bilateral hilar or tracheoadenopathy with minimal or no symptoms (in such patients the disease usually follows a benign course); patients who have nonprogressive pulmonary lesions, with no or only minimal symptoms; patients who have fibrotic pulmonary lesions known to have been stable over a long period of time.

(*11*) The last question is: What is the etiology of sarcoidosis?—and we are still waiting to hear the answer to that.

RESEARCH ON GRANULOMATOUS DISEASES

CARL T. NELSON, *Moderator*

INTRODUCTION

DR. NELSON: During the program this morning, I believe it was Dr. Hardy who said that the granuloma is the hallmark of sarcoidosis, and even though it may not have a great deal to do functionally with the particular condition, I think this is a very apt expression.

I think that, if we knew the exact pathogenesis of the granuloma formed in sarcoidosis, we probably would know a good deal more about the etiology of the disease. It is for this reason, I suppose, that studies on the production of experimental granulomas, allergic granulomas, and Kveim-test granulomas are of some importance. They might help to unravel some of the mechanisms of this peculiar condition.

To my mind, the Kveim test affords the most direct way to study production of such sarcoidal granulomas in miniature, if you will, in their natural habitat. Some of us think more highly than others of the Kveim reaction or the Nickerson-Kveim reaction. I think those who like this test should be prepared to give their reasons, as should those who do not. We will try to bring them out this morning.

THE PRODUCTION OF EXPERIMENTAL GRANULOMATOUS LESIONS INDUCED BY INJECTIONS OF FATTY ACIDS AND FRACTIONS OF TUBERCLE BACILLI[1]

J. UNGAR AND P. W. MUGGLETON

INTRODUCTION

Pathologic changes are induced in guinea pigs after inoculating fractions of tubercle bacilli or of synthetically produced fatty acids closely related chemically to those occurring naturally in these organisms. In natural infections with *Mycobacterium tuberculosis*, the lesions produced are the result of the actions of living bacteria, bacterial debris, and disintegrated soluble cellular components (proteins, lipopolysaccharides). These local lesions are also considerably influenced by the degree of allergy to bacterial constituents acquired after about three to four weeks.

Proteins, nucleic acids, polysaccharides, and lipids may be isolated from mycobacteria. Anderson (1) has described three types of lipid: acetone insoluble matter; acetone-soluble fats; and chloroform-soluble waxes, separable into (*a*) soluble, and (*b*) insoluble in ether-methanol mixture.

Most of the waxes are present as esters of hydroxy fatty acids with alcohols or as lipopolysaccharides. The so-called "mycolic acid" is a hydroxy fatty acid; the acid-fastness of the tubercle bacillus has been attributed to it (2). According to Lederer (3), Bloch's cord factor, a lipopolysaccharide isolated from tubercle bacilli by light petroleum extraction, is an ester of mycolic acid with trehalose. Choucroun (4) isolated a lipopolysaccharide from tubercle bacilli by extraction with heavy paraffin oil, and this substance (PmKo) was studied in the investigation reported here.

Sabin, Doan, and Forkner (5) and Sabin, Smithburn, and Thomas (6) made the first systematic attempts to produce experimental lesions in animals with fractions of tubercle bacilli. Later, studies were extended to include analogous synthetic substances (3, 7).

This report deals with the granulomatous lesions produced by a synthetic analogue of phthioic acid, as well as the actions of heat-killed tubercle bacilli. The acid has been studied previously (8, 9).

MATERIAL AND ANIMALS

In studying the effect of injecting naturally occurring and synthetic fatty acids into experimental animals, guinea pigs were chosen because of their high degree of susceptibility to *Mycobacterium tuberculosis*. Albino animals weighing about 250 gm. were used; the substances were generally injected either intraperitoneally as suspensions in alcohol-saline or were dissolved in ether. In a few experiments they were given subcutaneously.

[1] From the Glaxo Laboratories Ltd., Greenford, Middlesex, England.

Experiments were carried out with four substances, viz:

(*1*) Heat-killed *Mycobacterium tuberculosis* (var. *hominis*). The suspension was heated at 65° C. for one hour; it contained 5 mg. (moist weight) in 1 ml. of saline.

(*2*) Choucroun - type lipopolysaccharide (PmKo).[2]

(*3*) Synthetic methyl substitute of a long-chain fatty acid, 3:12:15-trimethyldocosanoic acid (TRC 270), prepared by Dr. Polgar (Oxford). Injected in 0.1 ml. of ether.

(*4*) Mycolic acid was prepared[3] and injected in 0.1 ml. of ether.

Each substance was injected at several concentrations into groups of 6 guinea pigs. At regular intervals (three, seven, twelve, and twenty-eight days, six weeks, and three months) guinea pigs from each group were killed. Autopsies were performed and specimens were taken for histologic examination.

Results

Small lesions were seen in guinea pigs after intraperitoneal injection of 10 mg. of the compound TRC 270, but marked lesions were found after injection of 25 mg. A brief description of the lesions in guinea pigs after the injection of 25 mg. of this compound is given and is representative of the many recorded.

Results after eight days: Eight days after the intraperitoneal injection of 25 mg. of TRC 270, a hard waxy deposit on the spleen and omentum was seen, together with perisplenitis, enlarged mesenteric lymph nodes, and waxy deposits on the liver.

Results after fourteen days: After fourteen days white round nodules 4 to 5 mm. in diameter were seen fixed on the peritoneal wall. The omentum retracted towards the spleen, showing nodules of cheeselike consistency. The preaortic lymph nodes were enlarged, and small nodules were present in the liver, spleen, and occasionally in the lungs.

Results after twenty-eight days: After twenty-eight days some soft round white bodies, 2 to 8 mm. in diameter, were found in the abdominal cavity. Nodules of cheeselike appearance in the indurated inflamed omentum were seen, and the omentum was often adherent to the spleen and kidney. The spleen was enlarged with perisplenitis, and the liver was adherent to the diaphragm. Nodules were present on the diaphragm; sometimes adhesions of the mesentery to peritoneal serosa were seen. Mesenteric and preaortic lymph nodes were enlarged. There were small nodules in the lungs, and the tracheobronchial nodes were enlarged.

Results after three months: After three months the omentum was thickened, fibrotic, and adherent to the spleen, which showed fibrotic changes in the capsule. The portal lymph nodes were enlarged, occasionally showing a small central

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[2] The extraction of lipopolysaccharide was carried out by the method of Choucroun (1947).

Heat-killed tubercle bacilli were freed from culture medium by repeated washing and filtration. The bacilli were freeze-dried and extracted for three days with heavy paraffin oil (s.g. 1.6–1.9), 3 ml. per gm. solid material, at 38° C., with gentle rolling of the containing vessel. The mixture was centrifuged (5,400 g, 8 hours) to give a clear brown supernatant. The residue was then extracted in a similar manner with 2 ml. of fresh paraffin oil, and the combined supernatants were treated with 7.5 volumes of dioxane (technical grade). The precipitate was collected by centrifugation (2,000 g, ½ hour), washed with dioxane (to remove the last traces of paraffin) and methanol. The residue was then treated with chloroform containing 5 per cent methanol and centrifuged. The supernatant was evaporated under reduced pressure to dryness and then extracted under reflux with light petroleum (60°–80° C.). This petroleum extract was evaporated to dryness under reduced pressure to give PmKo.

The analyses of two batches of material produced in our laboratory were similar to that of a batch produced in Dr. Choucroun's laboratory, except that our figures for nitrogen (0.74 per cent and 0.9 per cent) were lower than those for her material (1.05 per cent).

In preparation for injection, the PmKo is dissolved in ether, with the addition of phenol solution (0.5 per cent) containing a trace of Tween® 80. The mixture is blended by a short exposure to ultrasonic waves and the ether removed by distillation under reduced pressure.

[3] The crude wax was obtained from tubercle bacilli by chloroform extraction (yield 11 per cent of dried bacilli). It was dissolved in ether and precipitated with methyl alcohol to give "purified wax." The "purified wax" was treated with hot acetone and then with a mixture of ether and hot acetone until no more substance was leached out. The liquid extracts were evaporated to dryness, and the residue was dissolved in ether. Acetone was added (equal volume) and the precipitated wax was collected (melting point, 55°–56° C.).

The precipitated wax was saponified in benzene/alcoholic potassium hydroxide to give mycolic acids, phthiocerol, and high molecular-weight fatty acids.

Mycolic acid can also be obtained from the lipopolysaccharide PmKo by alkaline hydrolysis to yield mycolic acid and carbohydrates (including mannose and glucose).

caseous mass. The liver showed a few small nodules. The mesenteric nodes were enlarged, and occasional enlargement of peritracheal lymph nodes was seen.

Twenty-four hours after 10 and 25 mg. of TRC 270 in alcohol-saline had been injected intradermally into guinea pigs, a local reaction was visible in the form of erythema and central induration, which gave rise in the next three days to a marked nodule in the skin and caused the breakdown of epidermis and discharge in some guinea pigs. These nodules persisted for ten to fourteen days and gradually disappeared.

Mycolic acid injected into the peritoneal cavity formed soft deposits in the first few days, and the general reaction suggested that the substance was more irritating than TRC 270. PmKo was more toxic than TRC 270. After an injection of 25 mg. of the substance, the guinea pigs were obviously ill, and some died after an injection of 50 mg. Those surviving developed lesions similar to those described as caused by TRC 270. After injecting heat-killed *Mycobacterium tuberculosis*, the later changes were also similar to those after injecting TRC 270. The bacilli elicited classical tubercles at an early stage, whereas fatty acid lesions at early stages were of the foreign-body foam-cell granuloma type.

The sections of organs showed characteristic histologic changes. In the early stages, three days after the injection of the synthetic acid TRC 270, small areas of patchy fibrinoid necrosis were seen in the omentum, occupying the stroma in the fat tissue. There were also large necrotic areas, some ill defined and some well defined. Most occurred in granulomas attached to organ capsules. They were separated from neighboring structures by flakes of fibrin membrane or by omental fat tissue.

After six to eight days, multiple, occasionally large, abscesses in the omentum were seen, with a collection of mononuclear cells (macrophages), beginning at the periphery. Many of these cells had assumed a distinct foamy appearance, obviously due to absorption of fatty substances. In some instances, patchy fibrinoid necrosis was predominant, the omental fat still being recognizable, as described at the three-day stage. There was also polymorphonuclear cell immigration into the necrotic patches.

Later, after ten to fourteen days, besides the abscesses, areas of necrosis, and peripheral collection of foamy macrophages, a few syncytia were seen engulfing disintegrating fat cells, and also the beginning of fibrous encapsulation in the periphery. Occasionally in the periphery of abscesses, a nodular arrangement of macrophages and syncytia became discernible.

At four weeks, the omentum showed encapsulated abscesses or areas of necrosis with patchy calcification and also foam-cell nodules and foreign-body granulomas at the periphery. Nodules of foam cells with central necrotic patches were seen in subcapsular areas of liver and spleen and lymph node, sometimes assuming a resemblance to tubercles. A few cells contained nuclei poor in chromatin and reminiscent of epithelioid cells and giant cells of the Langhans' type. Giant cells of the foreign-body type and syncytia, apparently formed by the confluence of macrophages, were also present.

At six to eight weeks, the omentum showed granulomas, mostly of the foreign-body type, surrounding large areas of necrosis, as well as small necrotic patches. The necrotic area had fibrous capsules and calcified patches, often with the shape of antlers, not unlike those seen in calcifying tuberculous foci. The spleen showed a cellular pulp and necrotic areas, some already encapsulated, others well demarcated by a zonal collection of necrotic polymorphonuclears. The liver at this stage showed a number of nodules consisting of hyaline collagen (scars) and sheets of foamy macrophages mixed with lymphocytes between them, the latter increasing in number toward the periphery, where they formed a line of demarcation.

In the skin twelve days after subcutaneous inoculation of heat-killed *Mycobacterium tuberculosis*, a sheet of granulomatous tissue was seen under the panniculus carnosus, consisting of macrophages, histiocytes, fibrocytes, mononuclear cells, and multinucleated giant cells. Most of the last named were large and many contained vacuoles, thus resembling foreign-body giant cells.

After ten to fourteen days, PmKo produced several granulomas in the omentum consisting mainly of histiocytes and macrophages and surrounded by young fibrous tissue. Numerous large multinucleated foreign-body giant cells were seen, many of them containing cleftlike or round spaces. Many large clefts occurred throughout the tissue, some containing a structureless, basophilic mate-

TABLE 27

CHARACTERISTIC CHANGES IN HISTOLOGIC SECTIONS

Material	Time	Dose	Route	Tissue	Reaction					
					Macrophages	Histiocytes	Giant Cells	Endothelioid Cells	Fibrocytes	Necrosis
	days	*mg.*								
HKTB*	12	10	i.p.†	Omentum	+++			+	+	+
	10	25	s.c.‡	Omentum	+++	++	+		+	+
				Liver	+				+	
	12	12.5	s.c.	Skin	+	+	+		+	
PmKo	10	20	i.p.	Liver			+		+	+
	10	50	i.p.	Omentum	+	+	++	+	+	++
	7	10	s.c.	Skin	+	+	+			+
TRC 270	10	25	i.p.	Omentum	+	+	++	+	+	+
				Liver		+			+	
	19	25	s.c.	Skin					++	
Mycolic acid	12	10	i.p.	Liver		+	+		+	+
	19	25	i.p.	Omentum		+	++			+
				Liver		+	++			+

* Heat-killed tubercle bacillus
† Intraperitoneally
‡ Subcutaneously
+++ = Large numbers present
++ = Moderate numbers present
+ = Few present

rial. Large necrotic areas were present, packed with nuclear debris, and occasional endothelioid cells were seen.

The main characteristic changes seen in the histologic sections are shown diagrammatically in table 27.

The sequence of changes in guinea pigs has shown a fairly typical picture after inoculation of the more active compounds. During the first few days, there were scattered small foci of necrosis succeeded by leukocytic immigration (which later resulted in either softening and abscess formation or patchy calcification). Seven-day-old lesions showed macrophages (mononuclear cells, histiocytes) appearing on the periphery of the foci. They were large and distinctly foamy, indicating absorption of fatty substances. Macrophages were seen ten to fourteen days later arranged in nodules, some showing central necrosis (or an abscess); some were "tuberculoid," containing Langhans' cells; and others resembled foreign-body granulomas.

The lesions developed at the site of injection, and there was evidence of lymphatic spread from the primary deposit (in the omentum and serous capsules of abdominal organs) into adjacent organs (diaphragm, lungs), where infarcts, areas of necrosis, and granulomas were occasionally found.

The changes are consistent with those found after injecting lipoid substances. Some of them resembled tuberculous lesions, but differed, particularly during the initial stages, from the lesions found after injecting suspensions of *Mycobacterium tuberculosis*. This difference can be attributed to the presence of organized acid-fast material (bacterial cells or granules), which does not occur in the aqueous suspensions, in oily solutions of the bacterial fractions, or in synthetic analogues. The type of cells in the lesions and the intensity of reactions depend on the chemical and physical nature of the substances, and particularly on the amounts injected.

The substances tested produced small foci of necrosis at an early stage after injection. This is in marked contrast to the necrosis and caseation seen in tuberculosis. These are later changes,

influenced to a large extent by the acquired hypersensitivity to bacterial products.

We regard the lesions produced by the fatty substances essentially as "foreign-body reactions," and hold that any resemblance to a specific granuloma at early stages of development of the lesions after inoculating the fatty extracts of *Mycobacterium tuberculosis* should be attributed to certain impurities from the bacterial extract. The amount of the fatty acids required to cause lesions is an important factor in differentiating between active and nonactive compounds. Many of the organic saturated and nonsaturated fatty acids of high molecular weight will cause a mild diffuse irritation that disappears in ten to fourteen days, but localized lesions will be formed only when large amounts (100 mg. or more) are injected. In contrast, the biologically active substances induce lesions after injection of comparatively small amounts (10 mg).

Finally, it should be mentioned that none of the fatty acids tested induced any allergy in the guinea pig, even after repeated injections.

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PINE POLLEN GRANULOMA IN ANIMALS[1]

RALPH A. VOGEL AND AGATHA M. THRASH

Introduction

The search for etiologic agents capable of causing granulomatous lesions has recently uncovered a suspect in the pine pollen. Cummings, Dunner, and Williams (1) noted a general similarity in the geographic distribution of pine forests and cases of sarcoidosis. The pine pollen is acid fast and contains lipid components capable of inciting localized epithelioid granulomas in animals (2). This interest in pine pollen has spurred extensive animal experimentation to probe its possible role in provoking tissue damage.

Methods

Saline suspensions of loblolly pine (Pinus taeda) were instilled in the nostrils of mice and guinea pigs, 3 to 4 drops in mice and up to 15 drops in guinea pigs. Two such treatments, a week apart, constituted the exposure to pine pollen. It was found necessary to lightly anesthetize the animals with ether to obtain deep penetration of the pollen into the respiratory tract. Animals were sacrificed at specified intervals and their tissues were examined histologically.

Special attention was given to staining techniques for detecting antigens and particles of the pollen in tissue. Fluorescent antibody was prepared from high-titered, precipitating rabbit antiserum to pine pollen, and the widely accepted techniques for fluorescent antibody staining in tissues were used. The auramine-rhodamine stain (3) for acid-fast material was also utilized to demonstrate pollen particles in tissue.

Results

Pathologic findings: Whole pine pollen was demonstrated in the bronchial walls and alveolar spaces two days after exposure. The bronchial epithelium was eroded and ulcerated in some areas which apparently allowed pollen to move into the lung parenchyma. The whole pollen and fragments thereof have been observed to travel to the smallest alveoli, although they tend to stay around the bronchi and organize into the sides of the bronchial mucosa. The pollen grains are surrounded by a subacute inflammatory reaction in the lung parenchyma. Neutrophils and large mononuclear cells actually infiltrate the pollen, as if in response to some chemotactic substance. No giant cells or epithelioid cells were encountered at this time.

Granulomas have been seen in both mice and guinea pig lungs two months after exposure to pollen. The granulomas do not differ from those seen in foreign body or other reactions in which there is not a strong necrotizing factor (figure 45). The tissue response at three months is essentially unchanged. Livers and spleens from these animals were normal. An interesting finding involved guinea pigs immunized endotracheally with a fat extract from pine pollen twelve months before intranasal challenge with whole pollen. Moderate to severe anaphylaxis occurred in these animals and, in comparison with nonsensitized pigs, they showed a more intense chronic inflammatory reaction with a striking eosinophilic component in some cases (figure 46). The development of these lesions has not been observed beyond three months; however, a long-term period of observation is in progress.

Animals exposed in a similar manner to ragweed pollen have been used as controls. While chronic inflammation was noted in these animals, it has been to a lesser degree, and to date no granulomas have been observed.

Specific staining of pollen in tissue: It was necessary to use frozen tissue sections for fluorescent antibody work since the reaction was inactivated by formalinization and deparaffinization procedures. In tissue from animals sacrificed in two to three days, fluorescent antibody stained the germinal center of the pollen grain but not the walls or bladder appendages. Several weeks after the administration of pollen, attempts to stain the antigen were unsuccessful. This was attributed to a dissolution of the outer pollen membranes and the solubilization or dilution of the antigen in the tissue.

The auramine stain was very effective in demonstrating large or small fragments of the entire covering of the pollen. The intense staining of the pollen made them easy to visualize, even when few particles were present. Particles were visible in animals sacrificed after three months. Formalin fixation and paraffinization procedures did not interfere with the staining reaction.

[1] From the Veterans Administration Hospital, Atlanta, Georgia.

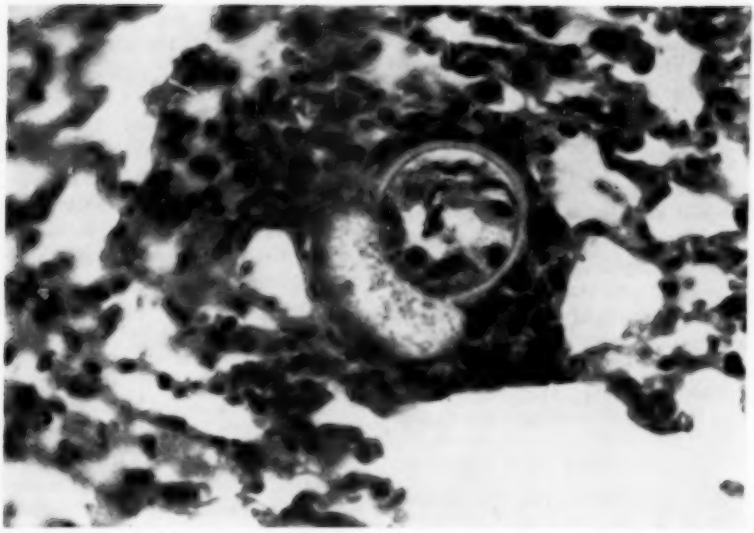

FIG. 45. Pine pollen in the lung of a guinea pig two months after intranasal instillation. There is a nonspecific, chronic inflammatory reaction around and inside the pine pollen grain. (Hematoxylin and eosin stain, × 460)

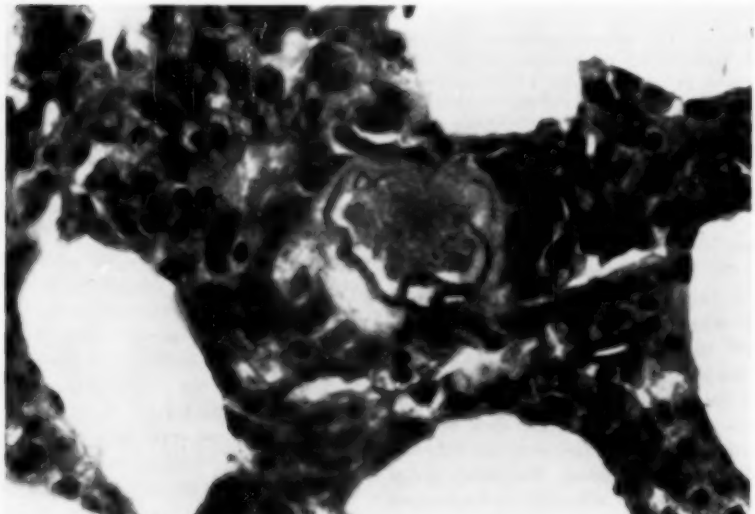

FIG. 46. Pine pollen in the lung of a guinea pig which was previously immunized with fat extract from pine pollen, one month after intranasal challenge with pine pollen. There is more dense fibrosis and chronic inflammation than in the unsensitized animal shown in figure 45. (Hematoxylin and eosin stain, × 460)

Ragweed pollen in tissue did not take up the auramine stain.

Discussion

The introduction of pine pollen into the respiratory tract of experimental animals with comparative ease, despite its large size (40 μ) should cause renewed speculation regarding the likelihood of air-borne allergens gaining entrance to the deeper recesses of the human respiratory tract. While the early lesions noted in the animal lungs do not resemble sarcoid lesions, a long-term period of observation will be necessary to make final comparative judgment. As suggested by these preliminary experiments, the hypersensitivity component may play an important role in evoking more extensive chronic inflammation.

The use of the auramine stain promises to be an effective tool for following the fate of the pine particles in tissue and also for searching human, formalinized sarcoid tissue for evidence of acid-fast residues or particulate matter resembling pine pollen. The fluorescent dye auramine has a strong affinity for tubercle bacilli, resisting decolorization with acid-alcohol, while other acid-fast organisms (including pine pollen) show a weaker binding of the dye and require treatment with 25 per cent sulfuric acid. The difference between tubercle bacilli and pollen staining noted here would tend to support the findings of Cummings and Hudgins (2) that the acid-fast material of pine pollen is not the same as mycolic acid, found in tubercle bacilli.

Summary

Guinea pigs and mice were given pine pollen intranasally under ether anesthesia. Pollen was observed in the alveolar spaces and around the bronchi. Chronic inflammation, noted in and around the pollen grains, was characteristic of a granulomatous reaction. Fluorescent antibody techniques identified the antigenic portions of the pollen, while auramine staining revealed small acid-fast particles of the pollen three months after introduction of the innoculum.

Acknowledgment

The writers wish to acknowledge the technical assistance of Mr. Peter Fedors, Medical Research Assistant, Veterans Administration Hospital, Atlanta, Georgia.

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THE BIOLOGIC SIGNIFICANCE OF EXPERIMENTALLY INDUCED ALLERGIC GRANULOMAS[1, 2]

FREDERICK G. GERMUTH, JR.

The injection of sufficient amounts of foreign protein into rabbits may lead to the development of a wide of variety of lesions (1–3). Following a single large injection of bovine albumin, acute arteritis, glomerulonephritis, and granulomatous lesions are frequently seen. These lesions develop during the immune phase of antigen elimination and regress after the antigen has been completely eliminated and free antibody appears in the circulation (3).

The character and distribution of these allergic lesions can be markedly influenced by the dosage of antigen and the length of antigen administration. Prolonged periods of sensitization by multiple injections of large quantities of antigen produce acute, healing, and healed arteritis in the absence of glomerular and splenic lesions (4). On the other hand, prolonged sensitization by small quantities of antigen may lead to the development of subacute and chronic glomerulonephritis in the absence of significant arterial lesions (5).

There is indisputable evidence indicating that the tissue changes produced by antigen administration are the result of the antigen-antibody combination. Recent work has demonstrated the important role played by circulating soluble antigen-antibody complexes in the initiation and localization of allergic lesions (6, 7). The development of lesions appears to be dependent on the antibody response and the amount of antigen administered. The ratio of antigen administered to the magnitude of antibody synthesis must be such as to allow the formation of soluble and biologically active antigen-antibody combinations. Large amounts of antibody lead to insoluble complexes which have little or no biologic activity. Thus, excessive antibody production tends to act as a protective mechanism (5).

Granulomatous lesions frequently occur in the spleen and lymph nodes of animals that receive a single injection of antigen (3). These lesions consist of accumulations of epithelioid and giant cells. In an occasional lesion, a central core of pink-staining "fibrinoid" debris is seen. In the spleen, this alteration is most prominent within and immediately surrounding the follicles. In the lymph nodes, both the cortex and medulla can be involved. The granulomatous lesions bear a marked resemblance to noncaseating, epithelioid, or "hard" tubercles.

There is considerable evidence that the extravascular granulomatous lesions have an immunogenesis similar to that of the vascular and glomerular lesions. These lesions occur during the period of active antigen-antibody interaction, and can be produced by the passive transfer of antibody in the presence of antigen (8). Although the mechanism by which antigen-antibody combination produces the granulomatous inflammatory reaction is not clear, it has been suggested that it is a foreign-body reaction resulting from the cellular removal and sequestration of large antigen-antibody aggregates (8).

It is not the intention of this presentation to suggest that the etiology of sarcoidosis is similar to that of the experimentally induced allergic granulomas. The significance of these lesions is that they appear similar to those seen in certain allergic disorders of man. Similar lesions have been encountered in polyarteritis nodosa resulting from hypersensitivity to drugs and in asthma (3). The occurrence of granulomatous lesions in allergic granulomatosis and Wegener's syndrome serves to classify these disorders as variants of polyarteritis nodosa. Perhaps the most basic concept to be gained by these studies is that granulomatous inflammatory lesions can result from hypersensitivity to soluble antigens.

[1] From the Charlotte Memorial Hospital, Charlotte 3, North Carolina.

[2] Condensation from original presentation with lantern slides.

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THE PREPARATION AND STANDARDIZATION OF KVEIM TESTING ANTIGEN[1]

MERRILL W. CHASE

As some of you may know, my interest in the cutaneous test for sarcoidosis arose through certain experiments in the laboratory. I was glad to join with Dr. Hirsch and Dr. Siltzbach in order to observe the development and types of nodules formed by patients with sarcoidosis in response to the injection of suspensions of sarcoid tissues. From this, I hoped to assess the validity of the doubts scattered in the literature regarding the test. From my actual observations, I am able to conclude that a class of persons exists who exhibit indubitable reactions to a properly chosen splenic preparation and not to equivalent preparations of normal spleen. In the Sarcoidosis Clinic of the Rockefeller Institute Hospital, I have examined nodule formation in 93 persons, and 204 nodules from these persons have been confirmed histologically as epithelioid cell tubercles. There can be no doubt that the so-called Kveim or Nickerson-Kveim test merits serious attention.

In the following report, the preparation of sarcoid tissue will be termed, loosely or perhaps in anticipatory sense, the test-antigen.

The problem appears to hinge on obtaining properly selected tissue, its preparation, and its distribution for practical use and study. A further question has to do with the nature of the active material contained in the tissue. Criteria for selecting sarcoid tissue that is suitable for the preparation of the test-antigen should include (*a*) a sufficiently high concentration of the active principle; (*b*) a sufficiently low concentration of substances that excite nonspecific inflammatory responses; (*c*) absence of agents of transmissible disease; and (*d*) availability of adequate supplies of tissue for proper determination of the first three points before acceptance for practical studies.

For these reasons, it seems best not to employ lymph nodes as a practical source of antigen for widespread use, since it is judged at the present time to be hazardous to pool material taken from different patients with sarcoidosis. Sarcoid spleens removed at operation for reasons of hypersplenism offer the desired large supplies of source material.

Failure of tissue to have a sufficiently high concentration of the active principle is known, and indeed such seems to have been the reason for certain unsatisfactory experiences reported in the literature.

Among undesirable properties in sarcoid tissues, we may list an ability to evoke inflammatory responses owing to factors presently unknown and occasional curious properties that undoubtedly reflect past experiences of the individual prior to development of his sarcoidosis. Such an instance, probably an extreme case, was presented by the abundant nodal tissue removed at operation from a patient in the Rockefeller Institute series. In patients who exhibited sarcoidosis and were anergic to the delayed type of hypersensitivities, the test-antigen prepared from these particular nodes gave positive Kveim tests, but with decided evidence of an early inflammatory component. In contrast, pronounced reactions of the delayed type occurred upon intracutaneous injection in normal persons who were reactive to tuberculin. When this test-antigen was divided into supernatant fraction and washed sediment, both portions elicited tuberculin-like reactions in a tuberculin-positive control individual, appearing within fifteen hours and lasting more than seven days. Also, this test-antigen gave rise to dermal reactions in guinea pigs that were hypersensitive to tuberculin. Obviously, tissues with such bizarre components are to be rejected as sources for test-antigens.

All new tissues, however, should be studied carefully before acceptance, by making a trial batch of test-antigen for evidence of an undue capacity to produce nonspecific inflammation, as well as for the ability to evoke granulomatous responses in patients with sarcoidosis. Such tests should be run in parallel with at least one known acceptable test-antigen, and comparison should be made at several concentrations of unknown and standard. Our practice is to use not more than two or three test sites per patient, and to extend the testing until an evaluation is reached.

[1] From The Rockefeller Institute, New York 21, New York.

The tissue should be handled, dispensed, and deposited in the cutaneous test site in such manner as to exclude the introduction of foreign bodies that can incite granulomas, i.e., cotton, sand, probably bits of rubber and sulfur-containing rubber from vial closures, and translocated bits of hair shafts and dermal plugs of the test subject himself. To minimize the incidence of foreign-body granulomas, the use of syringes and needles that are sterilized in glass with uncoated cellophane (P.D. No. 300) caps and No. 26-gauge, $\frac{3}{8}$-inch needles provided with Huber point and closed bevel is recommeneded.

Following is a report of the results of work done in collaboration with Dr. Louis E. Siltzbach.

Our first attempts at investigating a sarcoidal spleen consisted of teasings and centrifugings to produce 4 fractions: tissue, free cells, tissue particles, and solubles. Although several findings of interest resulted, we finally turned to the production of a "basic" type of test-antigen, and developed a system of handling splenic tissue with sterile technique in stainless steel chambers in the cold.

Thirty to 35 gm. of sarcoidal spleen are processed at one time by use of eight 50-ml. stainless steel centrifuge tubes. The scale can be doubled easily by employing two such sets during the work of the first day, and pooling the material into one set of eight tubes for the operations of the second day.

The steps in the preparation are as follows:

1. Thaw; tease; scissor.
2. Disintegrate stepwise in cold buffered saline.
3. Wash twice by centrifugation, 5,500 g. for twenty minutes.
4. Suspend, disperse, strain (40-mesh and 80-mesh sieves).
5. Adjust pH (one-drop glass electrode on side portion).
6. Heat 58° C. for seventy-five minutes on two successive days at pH 7.2 to 7.4.
7. Check sterility; ascertain alcohol-precipitable dry weight.
8. Phenolize bulk suspension at once.
9. Adjust concentration, check pH, dispense.

Special strainers are used, in which 4.3-cm. circles of stainless steel wire are mounted rigidly and permanently in holders of stainless steel provided with handles. The wire sizes include 40-mesh (that is, 40 wires to the inch) and 70 by 80-mesh. (For special purposes, still finer mesh is used on occasion, such as nickel "Lectromesh," 0.003 inches thick, 0.003 inches hole size[2] (1). The latter is a flat sheet designed for the mounting of objects under study by the electron microscope. Used with suspension of sarcoid tissue, some rubbing and stirring with the nickel spatula is needed, and occasionally the strainers need freeing by back washing with sterile saline. The final suspension can be taken up readily through 26-gauge needles.

The complete preparation requires three days, or one day longer than conventional 10-per cent suspensions. The first day requires approximately three hours, the tissue throughout being kept sterile and cold (0 to 4° C.). The compacted tissue in the 50-ml. SS tubes is kept frozen overnight. On the second day, approximately the same time is required before the final suspension is put into the 58° C. water bath. It is held overnight at 4° C., while a portion, precipitated with alcohol, is being dried in a vacuum oven over calcium sulfate for standardization. On the third day, the second and final heating is carried out, portions are removed for final sterility testing, the reaction is checked, and phenol is added to a 0.25-per cent concentration. Final adjustment of the concentration is then made with the use of phenolized buffered saline; the material is then dispensed in 1.5-ml. portions. It may be used as soon as the result of all sterility testing is known. The work is carried out in a cold room. The choice of equipment is such that the number of manipulations is not large; with the services of a competent worker trained in sterile technique, the hazard of bacterial contamination is hardly more than in the making of crude suspensions. To date, we personally have made five batches involving really extensive manipulations, and there has been no contamination.

The final product is termed by us "Type I." Several concentrations are prepared, viz., 6.0, 3.0, 1.0, 0.33, and 0.14 mg. per ml. When 0.15 ml. is employed as the test dose, the amounts deposited in the skin become, respectively, 900, 450, 150, 50, and 20 γ. The usual test dose is 450 γ and it exhibits perhaps the activity of 5-per cent crude suspensions of the same spleen, containing about 1,100 γ of alcohol-precipitable material. Upon progressive dilution, many patients still show characteristic nodule formation, but with decreasing diameter of the gross nodules and generally fewer and smaller granulomas on biopsy.

A word perhaps is in order about the amount of tissue products contained in so-called "10 per cent," or conventional whole tissue suspensions. The amounts of alcohol-precipitable material contained in 13 vials of antigens made by several workers from five spleens were determined. They were found to vary widely. Assuming 80 per cent of water and salts in the dense sarcoid spleens, a "10 per cent" suspension would contain about 20 mg. per ml. if all the tissue were subdivided. The process of subdivision being irregular, and one stage in the conventional process calling for brief settling in a cylinder, the actual alcohol-

[2] Jelliff Manufacturing Company.

precipitable contents were seen to vary widely. Except for spleen number 1, we could not tell whether the others seen were prepared as 10-per cent or 5-per cent suspensions. Nevertheless, the amount of protein that would be deposited as a test dose (0.15-ml. volume) varied from nearly 0.9 to 3.7 mg., and the average of all is more than 2.0 mg. It must be noted that the process of heating, coupled with the usually slightly acidic reaction, causes coagulation and precipitation of previously soluble proteins contained in the original spleen.

It is proper and necessary to ask whether the reduction in alcohol-precipitable dry weight in the making of Type I test-antigen is accompanied by a loss in active material as well as in hemoglobin, serum proteins, and a certain amount of cell sap and microsomal tissue elements that evidently come from disrupted cells. Among the fine cell particulates, termed Fractions "ADS" or "DS," is indeed a small amount of material that is active as test-antigen. About eight-ninths by weight of the small yield appears to be inactive tissue constituents. Comparisons of this sort do not lead to decisions except as small, submaximal doses are employed. After quite a few preliminary trials had been made by testing sarcoidosis patients with various amounts, the experiment was made on 3 additional patients exhibiting sarcoidosis. All were tested with typical quantities of suspensions used as standards upon presentation at the Sarcoidosis Clinic of the Hospital of the Rockefeller Institute. Examination at the end of two weeks by gross inspection indicated that the reaction capacity to Kveim antigen was adequate for the intended purpose. Therefore, the low concentrations of Type I test-antigen (not containing the finer particulates) were injected to deliver 21 γ, and in a third site 180 γ of Fraction ADS was supplied. The gross diameters and the histologic readings were comparable, by and large. From this, we conclude that 9 weights of Fraction ADS are required to equal the activity of 1 weight of Type I antigen. In view of the very small yield of Fractions ADS and DS, there appears to be no reason to retain this type of material in the making of Kveim test-antigen. Such decision permits the above-mentioned significant reduction in protein in the standard test dose of Type I test-antigen over that contained in whole 10-per cent suspension.

The knowledge that solubles and fine particulates can be discarded allows the making of equivalent control preparations from normal spleens. Since such spleens are engorged with blood, control test-antigens made on the basis of whole 10-per cent suspension will consist largely of heat-coagulated serum proteins and hemoglobin. Splenic material, therefore, is cut into long narrow strips, rinsed of surface blood with sterile saline, and frozen in screw-capped tubes. The consequent rupture of erythrocytes on thawing, liberating hemoglobin and erythrocyte stromata, permits subsequent separation of the unwanted content of blood.

It is anticipated that Type I test-antigen will undergo further development. Its present form is designed in part for recognizing any dispersal of active material from tissue into the supernatant that may be effectuated by other types of manipulation. The activity of Type I test-antigen as a diagnostic tool will be presented by Dr. Siltzbach in the following paper.

CURRENT STATUS OF THE NICKERSON-KVEIM REACTION[1, 2]

LOUIS E. SILTZBACH

Although the specificity of the Nickerson-Kveim intracutaneous test for sarcoidosis, first described in 1941, has been questioned in the past, the test is gaining wider acceptance as its use increases. The scarcity of properly screened test material and some difficulty in deciding exactly what constitutes a positive microscopic reaction have impeded its definitive appraisal.

Continuing experience with the Nickerson-Kveim test at the Mount Sinai Hospital (1) and more recently at the Hospital of the Rockefeller Institute, involving 850 patients (almost half of whom had sarcoidosis), has confirmed our favorable opinion of its diagnostic worth. We consider the test reliable and simple enough to be carried out on an outpatient basis. The test is performed by us on all patients suspected of having sarcoidosis whether or not epithelioid-cell granulomas have been found on organ biopsy. A microscopically positive Nickerson-Kveim test has shown itself to be virtual proof of the diagnosis of sarcoidosis. Use of the test is resulting in some shift of diagnostic responsibility since the pathologist is now being called upon to share a role which formerly the clinician had to play almost alone.

With the presently available test materials, about 3 of 4 patients with active sarcoidosis are responsive to the test. It is not known why one of 4 fails to respond. The chief question is whether so-called "false-positive" reactions are exhibited by persons without evidence of sarcoidosis. In our hands, less than 2 per cent of such persons have shown positive reactions. This may be considered a satisfactorily low incidence of false-positive reactions in a biologic test.

Gross Reading of Nickerson-Kveim Test

The evolution of the gross nodule has often been described elsewhere (2, 3). Briefly, the nodule in a positive test begins to assume some shape in seven to ten days, rising above the skin surface in about fourteen days, and becoming dusky red brown as it grows. The nodule then grows firmer and larger, reaching a diameter of about 3 to 8 mm. in four to six weeks, when biopsy is usually performed. If it is allowed to remain, it slowly recedes, sometimes flaring up when the disease exacerbates. Some patients are able to produce nodules even while receiving steroid therapy, but the nodules appear to recede more rapidly once formed. Unbiopsied nodules which have regressed may show sudden recrudescence after steroid therapy is terminated or in the postpartum period.

Microscopic Reading of Test

In interpreting the test, we rely exclusively on the histologic pattern to determine whether a Nickerson-Kveim test is positive. It is our practice to remove palpable nodules at four to six weeks after injection, and we search carefully by oblique light for even slight elevation of the skin after moistening the skin with alcohol. We agree with Nelson (4) that it is not necessary to perform a biopsy when no nodule appears. But nodules 2 mm. and larger may fail to display histologically the characteristic granulomatous picture, and may show, rather, a nonspecific or foreign-body inflammatory change. For this reason, with the present test antigens, it is recommended that palpable nodules at the test site be removed for microscopic examination.

In reading the microscopic sections, I use criteria first worked out in 1946 in collaboration with Dr. Joseph C. Ehrlich, Director of Laboratories, Lebanon Hospital, New York (1). In a positive test spherical nodules are seen, composed mainly of epithelioid cells with occasional giant cells. A few lymphocytes and other inflammatory cells are visible within the granuloma in various amounts. The tuberculoid nodules may coalesce and give a picture of a diffuse, densely packed epithelioid-cell infiltration. But, nonetheless, at its periphery, discrete tuberculoid structures are usually found, arranged in satellite fashion. Small areas of fibrinoid change in the granuloma are not uncommon. They simulate those seen in the spontaneous lesion.

[1] From The Mount Sinai Hospital, New York 29, New York.

[2] These studies were supported in part by a research grant (E-2272) from the Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service.

With time, the Nickerson-Kveim test site assumes a blander histologic appearance, simulating more closely than a younger test site the appearance of a spontaneous sarcoid lesion. Two Nickerson-Kveim test sites removed thirteen and seventeen months, respectively, after injection showed clear-cut nests of epithelioid cells with some fibrous encapsulation. After seventeen months, some hyalinization had taken place in the scar tissue adjoining a granuloma mimicking the regressive changes seen in older spontaneous lesions of sarcoidosis.

Microscopic Findings in Negative Test Sites

Negative Nickerson-Kveim tests may also show local changes of varied patterns. These most often consist of banal inflammatory foci around blood vessels in the corium made up of lymphocytes and histiocytes sometimes containing brown pigment. Collections of foreign-body giant cells are also seen, and polarized light is necessary to detect the birefringent crystalline and fibrillar foreign material which giant cells enclose. It is still unclear whether these foreign bodies have an extraneous or endogenous source or whether they are of mixed origin.

Occasionally epithelioid cells are encountered in a test site in small numbers scattered through the dermis in a loose and haphazard arrangement lacking a true tuberculoid pattern. They are difficult to interpret. Such changes are considered equivocal and nondiagnostic, and the test is repeated.

Histochemical Studies

We have made a few preliminary histochemical studies of two sarcoid lymph nodes and two 28-day-old excised Nickerson-Kveim test nodules. The granulomas of both the spontaneous and the induced lesions showed positive staining reactions for neutral mucopolysaccharides, acid polysaccharides, phospholipids, and acid phosphatase. Both lymph nodes and test areas were negative to stains for fibrin, neutral fat, and amyloid. Feulgin and methyl-green pyronin stains were not contributory. Reticulin stains showed fibrils surrounding the granuloma and extending centrally in both types of granuloma, and eventual hyalinization of the granulomas was also alike in pattern.

The granulomas in the lymph nodes and in the test areas exhibited small areas of fibrinoid change. Neutral and acid polysaccharides were present in these areas.

The similarity of the histochemical staining qualities of the granulomas in the induced and spontaneous lesion, as well as the parallel evolution of the regressive changes in the healing phases of both lesions, lend support to the view that the tissue suspensions used in the Nickerson-Kveim test contain the same material which is responsible for inciting the granulomas represented by the spontaneously occurring lesions of the disease. What gives the Nickerson-Kveim test its special value is its high specificity which stands in contrast to the nonspecific appearance of the spontaneous granuloma of sarcoidosis.

Comparison of Type I Antigen With Whole Tissue Suspensions

Type I antigen described by Dr. Chase is, at present, the standard test agent used at the Mount Sinai Hospital and at the Hospital of the Rockefeller Institute. We compared the activity of our Type I antigen and the conventionally produced whole tissue suspensions made from the same spleen in order to be certain that the washed antigen was competent. We injected equivalent as well as unequal concentrations of each. Twenty-three suitable subjects exhibiting sarcoidosis received one or more intracutaneous injections of Type I antigen and the whole tissue suspension. In 9 patients the nodules were larger with the whole tissue suspension than they were with Type I antigen. Eight patients responded equally well to both; 6 patients were more sensitive to Type I antigen. In fact, Type I antigen showed minor loss of efficiency as a test agent when compared with its parent material.

Filtration of Microsomal Particles

As you have heard from Dr. Chase, subcellular particles removed in the washings of the splenic tissue had about one-ninth as much activity as their weight in Type I antigen. The total yield of the finer particulates, however, was so small in relation to the yield of Type I antigen that their removal may be considered inconsequential. These particles were indeed small enough to pass through an ultrafine fritted glass bacteriologic filter, and a small amount of satisfactory testing material could be recovered from the filtrate by ultracentrifugation, washing, and redispersal in

small volume. This finding explains the two positive tests produced with filtered material by Sones and associates (5).

When the filtered fractions were injected intracutaneously side by side with equal concentrations of the unfiltered fractions into 7 responsive patients, grossly and microscopically positive tests resulted at both sites in all 7 patients.

Clinical Results at the Mount Sinai Hospital

The results of our clinical experiences are summarized in tables 28 and 29. These data demonstrate the satisfactory level of specificity and sensitivity of the test agents used.

The Mount Sinai Hospital patients are classed into three groups: first, those with organ-biopsy-confirmed sarcoidosis; second, so-called "suspects"; and third, those with diseases other than sarcoidosis including tuberculosis, the so-called "control" group. Positive tests were recorded in 83 per cent of the patients of the biopsy-confirmed group and in 50 per cent of the "suspects." The majority of patients in the "suspect" group had clinical sarcoidosis but lacked organ-biopsy confirmation. For the remaining "suspects" the diagnosis was less certain. These included patients with undiagnosed lung disease, hepatosplenomegaly, isolated uveitis, or parotitis usually associated with hypergammaglobulinemia and negative tuberculin tests.

There were two "false-positive" tests recorded among the 267 patients with nonsarcoid conditions, less than 1 per cent. In addition, not shown, are microscopically equivocal tests which occurred in about 5 per cent of tests performed in all three classes of patients. These equivocal tests had to be repeated.

TABLE 28

NICKERSON-KVEIM TEST (650 PATIENTS)
THE MOUNT SINAI HOSPITAL, NEW YORK, NEW YORK, 1946–1960

Group	Number of Patients	Positive Tests	
		Number of Patients	Per Cent
Sarcoidosis; organ-biopsy confirmed	144	120	83
Sarcoidosis suspects; organ-biopsy result negative or not available	239	120	50
Other diseases, controls	261	2	1

TABLE 29

NICKERSON-KVEIM TEST (207 PATIENTS)
THE HOSPITAL OF THE ROCKEFELLER INSTITUTE, NEW YORK, NEW YORK, 1957–1960

Group	Number of Patients	Positive Tests	
		Number of Patients	Per Cent
Active sarcoidosis, subacute	71	54	76
Active sarcoidosis, chronic	45	29	64
Inactive sarcoidosis	6	2	33
Disseminated lung disease, cause unknown	42	6	14
Tuberculosis and other diseases	33	1 (?)	?
Schizophrenia, tuberculin negative	10	1 (?)	?

Clinical Results at the Hospital of the Rockefeller Institute

In the series of patients being observed by Dr. James Hirsch and his staff at the Hospital of the Rockefeller Institute, the patient material has been grouped into six classes (table 29).

The classification is based on an assessment of all pertinent clinical data, including the organ-biopsy findings whenever they were available. The result of the Nickerson-Kveim test was not disclosed to the clinician in order that the diagnostic grouping would not be influenced by such information. The Nickerson-Kveim tests, moreover, were read independently by two observers without knowledge of the clinical findings.

The table shows that the highest percentage of positive Nickerson-Kveim reactions was recorded in the group of patients with active *subacute* sarcoidosis, i.e., among those with lesions of less than two years' duration (76 per cent positive). Below this was the group with active *chronic* lesions of more than two years' duration (64 per cent positive). The lowest rate of positive reactions occurred in the 6 persons classed as clinically inactive (33 per cent). It is clear that the patients of the more recent cases have a higher proportion of positive reactions than the older ones.

In patients grouped under the heading of "disseminated lung disease, cause unknown,"

TABLE 30

REPEAT NICKERSON-KVEIM TESTS (IN 73 PATIENTS ORIGINALLY POSITIVE—135 BIOPSIES)

THE MOUNT SINAI HOSPITAL, NEW YORK, NEW YORK

Time Interval	Number of Patients	Per Cent With Positive Tests
2–5.9 months	28	86
6–11.9 months	23	78
1–1.9 years	22	68
2–2.9 years	19	58
3–3.9 years	13	54
4–13.9 years	19	42
Total: 2 months–13.9 years	73	61

mainly patients with pulmonary fibrosis and asymptomatic lung nodules, 14 per cent had positive reactions. In this group the Nickerson-Kveim test appeared to be detecting isolated chronic pulmonary sarcoidosis but this could only have been verified by open lung biopsy, which these patients had not undergone.

The "control" subjects have been divided into two groups. The first of these groups of patients had active and arrested tuberculosis and included as well a few instances of beryllium poisoning, histoplasmosis, systemic lupus erythematosus, and rheumatoid arthritis. One patient with tuberculosis had a questionably positive weak Nickerson-Kveim reaction but, unfortunately, the subject could not be retested. The other group of "controls" included 10 patients whose chest films were recorded as normal and the tuberculin tests negative. In order to study such a group, it was necessary to use patients with schizophrenia. One patient in this last group had a dubiously positive reaction but, unfortunately, we were not able to study this patient further.

There were possibly two "false-positive" tests among 43 persons having no evidence of sarcoidosis. Added to the two "false-positive" tests encountered among the "controls" in the Mount Sinai Hospital series, the incidence of "false-positive" reactions is less than 2 per cent.

The figures given in the two tables are wholly consistent with most published reports of the Nickerson-Kveim tests performed in large series by workers in Norway (3, 6), Denmark (2), Great Britain (7), New Zealand (8), and the United States (9, 10). These data have been reviewed elsewhere (11).

Repeated Nickerson-Kveim Tests

How long does a patient with a positive Nickerson-Kveim reaction retain his reactivity to the testing suspensions? In 73 patients showing a positive reaction upon the initial test, we were able to repeat the intracutaneous test one or more times at random intervals ranging from two months to thirteen years. These 73 patients received 135 sets of tests in which usually two different antigens or different concentrations of the same antigen were employed. Among retested patients, a higher proportion exhibited *chronic* lesions of sarcoidosis than was seen in the entire series of active cases because patients with chronic lesions are more likely to attend our clinic for many years, and therefore afford us the opportunity of retesting.

That there is a gradual loss of reactivity to the testing suspensions with time is indicated in table 30. Whereas only one in 7 had lost his reactivity by the end of 6 months after an originally positive response, more than half of the reacting patients had become unresponsive when tested between four and thirteen years later. The loss of reactivity often paralleled the clinical evidence of regression. However, many patients with clinical quiescence retain their positive Nickerson-Kveim reaction, pointing up the difficulty of determining when the disease process has truly abated. In the entire group retested, 61 per cent retained their reactivity and 39 per cent had lost it.

One patient with chronic cutaneous sarcoidosis was tested six times in thirteen years, and consistently reacted even while receiving steroid therapy. Another patient exhibiting chronic pulmonary and hepatic lesions which slowly underwent regression continued to show a positive response over an eleven-year span, and lost his responsiveness in the thirteenth year. Patients with chronic cutaneous lesions remained responsive to the test for long periods.

It must be pointed out that patients who have lost their reactivity, or who have not responded to the test initially, may still show granuloma in their organs on biopsy. But, in the majority of instances, loss of reactivity to the intracutaneous test and regression of the granuloma in the tissues go hand in hand with clinical recovery.

Summary

Agreed-upon methods of preparation of test suspensions is essential. International exchange

of tissues and test suspensions is suggested for the purpose of comparing the reactivity of patients with sarcoidosis in different areas and for determining the relative activity of tissues from these areas as sources of test substances. Testing a few patients in various geographic areas with suspensions derived from a single source has given fairly uniform results. This suggests that the disease may be the same in widely separated regions.

Nickerson-Kveim tissue suspensions made in New York City by us (Type I antigen, in the main) have already been tested in Florida, on a small scale in Puerto Rico, as well as in other parts of the United States. The results, on study of sections of the excised test sites sent to us, do not appear to differ from those obtained with Negro and white patients observed in New York City.

The tissue of a single patient, provided the concentration of the specific factor or factors in it is satisfactory and the specificity has been demonstrated, indeed serves to test all patients exhibiting active sarcoidosis. If sarcoidosis were caused by more than one primary inciting agent, it would be expected that a series of sarcoid tissues would be required to screen for the presence of the disease, and for this there is no evidence. Therefore, it seems to us more likely that sarcoidosis is a single disease and not a syndrome.

The specific factor responsible for the characteristic granuloma appearing at the test site in patients with sarcoidosis remains unknown.

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TISSUE CULTURE OBSERVATIONS IN SARCOIDOSIS[1,2]

ANNA-LISA OBEL, HOLGER LUNDBECK, AND SVEN LÖFGREN

Lymph nodes obtained by Daniels' operation from patients with sarcoidosis were used for direct tissue cultivation. In the fibroblast-carpet, which after a few days surrounded the lymph node fragments, small areas developed where the fibroblasts were rounded off and had lost their processes. The cytoplasm was strongly basophilic due to large amounts of ribonucleotides. The cytoplasm contained uncolored or faintly eosinophilic inclusions which appeared like small granules or large homogeneous masses. Under phase-contrast microscopy, these inclusions stained bright red with Giemsa, and with periodic acid and Schiff reagent they were strongly PAS-positive. Histochemical investigations showed that the substance probably is a neutral mucopolysaccharide or muco- or glycoprotein.

This change in the fibroblasts occurs invariably in lymph nodes from patients with sarcoidosis but they have been found occasionally in lymph nodes removed from patients with diseases other than sarcoidosis as well. The change is consequently not specific for sarcoidosis.

Discussion

DR. NELSON: We will now attempt to discuss these six papers. It is a difficult job, and I think it would be best to ask selected persons to start each discussion. Dr. Shelley, Dr. Ungar presented his data on the production of experimental granulomas, and I wonder if you have any comments that you would like to offer?

DR. SHELLEY: Dr. Ungar's work is very interesting. We believe he has given us an example in animals of a colloidal type of sarcoid reaction or epithelioid reaction. As we see it, he has introduced various fatty acids, long carbon chain fatty acids, which are not easily metabolized by the guinea pig, and they are, in a sense, foreign bodies. The compounds were injected in an alcohol-saline suspension or in ether. Thus, they are not readily taken care of by the body fluids. We think that the tissue response is a foreign-body response, and that over a period of months this foreign material is metabolized with resolution of the lesions.

This reaction is in sharp contrast to the allergic type of granuloma that has also been discussed here. In viewing the work of Dr. Ungar in relation to sarcoidosis, I would believe that it has more pertinence to our understanding of the histopathology of tuberculosis.

Dr. Ungar's findings under the microscope do not appear exactly to mimic, as I see it, the picture of sarcoidosis. Perhaps I can do no more than stress the words of Dr. Siltzbach, who pointed out that we must be very rigid in our thinking of the histology of sarcoidosis. There should be clear-cut epithelioid tubercle formation before we can start comparing any finding directly with sarcoidosis. I think this has been the great pitfall in accruing comparable data on the Kveim test.

DR. LEBACQ: Were you able to obtain granulomas in the lungs of your guinea pigs, Dr. Ungar? When the reaction is complete, is it possible to relocate the inoculated agent at the site of the lesion, or do you think the agent stays where it is injected and that the granuloma is an allergy?

DR. UNGAR: I was very glad that Dr. Shelley said, more or less in a nutshell, what I think is the basis and development of these changes. That is, that these granulomas are nonspecific in their nature and based on a necrotic reaction which has nothing to do with allergy. My final remark was that an allergic phenomenon does not, in my opinion, come into this picture.

Regarding your question, Dr. Lebacq, I think we tried different methods of intravenous injection, and again the granuloma behaved as a foreign necrotizing substance. If you inject more, you kill the guinea pigs right away. If you give small doses in a fine emulsion or suspension, you can see deposits distributed over the body.

Regarding the fate of injected substances, I have shown here that the substance injected, perhaps subcutaneously or in a muscle, will cause a local lesion primarily and then spread through the lymphatics. We can follow the lesions according to the pathway of distribution in the body. The primary reaction is a necrotizing one. There is no evidence in our work that allergic phenomena come into the picture.

DR. NELSON: Dr. Cummings, you were going to say a few words about Dr. Vogel's paper on the production of pine pollen granulomas in mice.

DR. CUMMINGS: Dr. Vogel has succeeded where we failed, namely, in the introduction of particular matter into the mouse and guinea pig lung. In my judgment, this striking demonstration of Dr. Vogel's is of real importance, whether or not it throws any light on the pathogenesis of sarcoidosis.

[1] From the State Veterinary Medical Institute, the State Bacteriological Laboratory; and St. Göran's Hospital, Stockholm, Sweden.

[2] Summary of paper read by Sven Löfgren.

I was most impressed with his demonstration of antibody which could then be coupled with fluorescence to search out the antigen in the lung tissue. The application of the Coons technique, I think, proved to be very profitable here.

It was also comforting—to me at least—to learn that acid-fast characteristics of pine pollen could be confirmed using the auramine technique in lieu of the Ziehl-Neelsen technique. I think Dr. Vogel's demonstration is much more evident than our own. In this regard, Dr. George Baers of the Milwaukee General Hospital has demonstrated auramine fluorescent bodies in tissues obtained from patients with sarcoidosis. Whether or not they represent the same materials remains to be seen.

Finally, I think the demonstration of anaphylaxis in animals which had previously received extracts of pine pollen also proves to be of some real interest and importance. In this context, I would like to tell you of the work of others who have demonstrated a profound cytolytic effect of pine pollen extracts. Perhaps you may wish to ask Dr. Patnode to comment on this, but I understand he has demonstrated a cytolytic effect on leukocytes obtained from hypersensitized guinea pigs. From the clinical side of the coin, Dr. Herbert Seiker of Duke has recently reported selected cytolytic effects of pine pollen on leukocytes obtained from patients with sarcoidosis.

Whether we are dealing with pine pollen disease or something related to sarcoidosis, Dr. Vogel is to be commended for demonstrating these biologic and immunologic effects.

DR. NELSON: Dr. Hardy, what do you think of this material presented by Dr. Vogel and also by Dr. Ungar?

DR. HARDY: I do not feel competent to say anything about Dr. Ungar's presentation. That is not within my expertise. However, I am very much excited by Dr. Vogel's presentation. It seems a very interesting evolution of work, begun by Max Michael and John Gentry, which will help synthesize the epidemiologic evidence in our search for etiology.

I would like to make this comment because of my great interest in diseases of environmental origin. I see some difficulty in the idea of a particle 40μ in diameter getting into the lungs. I think you would have to anesthetize the animal in order to put material of such size in the lower respiratory tract. Workers interested in dust disease have shown that respirable material must be 10μ or smaller to reach the bronchioles and alveoli. Only a small percentage of particles of more than 10μ in diameter would get into the lungs, and then only if there were some defect in the defenses of the upper respiratory tract. What I am saying does not take away at all from the importance and interest of the things that Dr. Cummings has just said. However, in my opinion, it has a good deal to do with what can be said about the possible air-borne etiology of sarcoidosis on the basis of these animal studies.

The other thing that stuck in my mind was that we saw only localized pulmonary reactions, even after long periods of time. I hope the observers will find something of the order of magnitude that will get into the blood stream. I am one of those who believe that the disease we are talking about is a systemic disease—not a localized disease.

DR. NELSON: Dr. Chase, are you particularly surprised that a guinea pig or a mouse exposed to pine pollen should be found to be anaphylactic to this substance a year later?

DR. CHASE: No, that is not surprising.

I wish to ask one question of Dr. Vogel since a possible cause could be suggested for the pathologic changes that he observed. Dr. Vogel, do you know whether you can extract terpenes from pine pollen? If you can, the observed pathologic changes would represent precisely the kind of reaction that might be supposed to arise, provided the extract of pollen could be proved to be injurious directly. Can "terps" be extracted?

DR. VOGEL: I feel certain the pine pollen, itself, has "terps."

DR. CHASE: If the grains of pine pollen contained "terps," one could expect all of this granulomatous change but would expect it to be absent in the ragweed pollen lacking the irritant. "Terps," I believe, could also cause injury to the alveolar membranes, which might allow penetration of the whole pine pollen grain.

DR. VOGEL: The acid-fast character of it, I think, speaks for some sort of a tissue modifier.

DR. CHASE: A gram or so of pollen might be subjected to steam distillation to see whether some turpentine-like material is yielded. If so, special tests could be made with it, with regard to causing changes in alveolar membranes.

One other point may be mentioned: The problem of staining the external "shell" of pollen grains with fluorescent antibody has been encountered previously in analogous studies made with certain endoparasites. Here, fluorescent antibody usually "picks up" and stains certain inner organs of the parasites and fails to render the outer cell wall visible. But, on occasion, one finds an animal which produces antibody also to the outer cell wall, for this structure is antigenic even though it does not give rise to antibody with regularity, being only feebly antigenic. A serum may yet be discovered that will contain an antibody for the surface structure of the pollen grain.

DR. VOGEL: We have obtained better sensitized

animals, producing antibody that will fluoresce the entire shell.

DR. NELSON: Is auramine a specific stain for what we call acid-fast material?

DR. VOGEL: Some people believe it is due to mycolic acid. Dr. Richards does.

Dr. NELSON: Dr. Dunner?

DR. DUNNER: Dr. Hardy made a most important point relative to the size of the particles which can enter the lung. If it is true that a particle of this size can get into the lung only under anesthesia, this mitigates against the possibility of pine pollen's entering the lung. On the other hand, perhaps, we may have to change our concept about the upper size limit of such particles. Dr. Boren of Houston reports that, theoretically, particles of 100μ can get into the lung. I had a telegram yesterday from Dr. William Hentel, Albuquerque, New Mexico. Knowing of this meeting, he was repeating the work that Dr. Vogel has been doing. He reports that his specimens of autopsied guinea pig lung contain particles of 45 to 60μ.

I think we should keep our minds open as to the size of the particles that can get into the lung under various conditions.

DR. ISRAEL: May I insert for the record that, in studies we have carried out, pollen of Scotch pine was used on the theory that this is the only pine native to northern Europe. Because of this problem of size, the pollen was ground and introduced intratracheally in rats. Up to a year later we have observed no granulomas.

DR. NELSON: In anesthetized animals?

DR. ISRAEL: The rats were deeply anesthetized with ether, but for only a few minutes.

DR. ANDERSON: There are other portals of entry than the lung for pine pollen. Dr. Vogel lives in Georgia, and he knows that pine pollen is so thick on all surfaces that it could easily enter abrasions in the skin. Working with any object that is outside, you can get plenty of pine pollen.

DR. MICHAEL: Why do we have to get so upset about the particle size? Might it not be possible that pine pollen could lie somewhere along the tracheobronchial tree and portions of it be carried into the lungs?

DR. HARDY: The upper respiratory tract has all sorts of ways of seeing to it that large particles do not get past the turbinates. The ciliated epithelium and mucus trap what gets past the turbinates. Such material is then swallowed or spit out. Certain material may penetrate the nasal septum. There are many studies showing that the lower respiratory tract is well protected from foreign material.

DR. VOGEL: I wanted to address a comment to Dr. Israel about his surprise findings. In view of our pathologic findings, it is quite interesting that you came up with completely negative results. Did you examine the animals for pine pollen in the early stages?

DR. ISRAEL: There was a transient initial nonspecific inflammatory reaction.

DR VOGEL: I wonder if you have studied the pine itself.

DR. ISRAEL: No, we have not; but we will.

DR. NELSON: Dr. Germuth presented a very interesting and thought-provoking paper on the significance of experimentally induced allergic granulomas. Dr. Chase, will you comment?

DR. CHASE: Dr. Germuth's paper is well-nigh self-contained, with respect to intent, procedure, finding, and interpretation. There is no doubt that in antigen-antibody complexes he has found an adequate stimulus for the production of experimental granulomas in rabbits. The areas involved are sometimes rather small in extent, but are frequently sufficiently large for their acceptance as prototypes of granulomas.

I am, nevertheless, not at all sure that antigen-antibody complexes are the only agents that may evoke granulomas. Certainly, such histologic changes may be produced by chemical substances which have no known capacity to form antibodies.

There is one fact that I sought during Dr. Germuth's presentation. Perhaps he would tell us about the rapidity with which epithelioid cells are formed. Granted that, when antigen alone is given to rabbits suitable for the experiment, antigen is in course of disappearance within the first six days, and that arteritis and nephritis are increasing to the maximum in the latter part of this period prior to detection of antibody in the serum. We would inquire as to the time when rabbits exhibited granulomas after treatment with antigen and antibody complexes. I refer both to animals receiving preformed precipitates of antigen and antibody and to those which were infused with antibody for a period of forty-eight hours, started immediately after injection of antigen.

I would add that Schwab and Cromartie have been able to produce granulomas in rabbits in a yet unexplained way by the intradermal injection of certain strains of streptococci. Although on occasion, as I recall, granulomas were found at five days, the great bulk of their experience indicated that the granulomas require about thirteen days to form.

DR. GERMUTH: In an experiment comprising 80 to 100 animals with active serum sickness that were killed in 2-day intervals, we never saw granulomas until after the sixth day. At that time antibody started to be made, as reflected by the antigen disappearance curve. After infusion of

antibody in an animal that had antigen, granulomas were seen usually beginning about thirty-six hours afterward.

DR. CHASE: In your average experience, when are the granulomas seen to be best developed?

DR. GERMUTH: Do you mean in active disease?

DR. CHASE: Either experience would furnish a useful example.

DR. GERMUTH: Well, they are best developed in ten to twelve days. Actually, that is it in most of them.

DR. UNGAR: It seems to me that the concept is a very interesting one, but I am afraid that it is very difficult, and perhaps very often misleading, to deduce the cause from a resemblance to certain pathologic changes. We have had a very nice exhibition of what sensitivity in relationship to cause and disease can do, but what I have learned about sarcoidosis does not seem to resemble the changes Dr. Germuth has described in his investigation.

DR. NELSON: You are not prepared to say or believe, then, that sarcoidosis is the result of antigen-antibody union?

DR. UNGAR: Not on the classical system that has been given to us.

DR. GERMUTH: I would like to say that I did not mean to imply that sarcoidosis was due to the protracted type of anaphylaxis that we have been working with. I merely wanted to show you that it was possible to get granulomas as a result of antigen-antibody interaction.

DR. ZIMMERMAN: I would like to ask Dr. Germuth two questions. First, I know that in this type of work the antibody has been demonstrated in the lesions by the Coons technique, but I wonder if they had been demonstrated also in the epithelioid cells or in the granulomas?

My second question is in relation to Dr. Shelley's earlier suggestion that we have two different mechanisms for formation of epithelioid cells, one dependent on allergy and the other produced by colloidal substances. I wonder if all of these can be resolved into the concept of colloidal substances. Perhaps when Dr. Germuth obtains the same granulomatous lesions by his techniques, it is because they are taken up by certain cells in the tissues as colloidal substances, as in Dr. Shelley's complexes. Could this be the common denominator? This, of course, relates to the question that pathologists always ask: What makes a macrophage transform into an epithelioid cell?

DR. GERMUTH: First of all, as you know, Dr. Zimmerman, gamma globulin, which is not a specific antibody but has been equated to antibody, has been demonstrated in a variety of lesions, and we have been able to demonstrate it in the spleen. Your second idea, whether this is a foreign-body type of granulomatous reaction, is an interesting one. However, in our recent work with rats, we are not seeing granulomatous lesions, even though the antigen-antibody reaction leads to colloidal aggregates.

DR. UEHLINGER: You have discussed two stages of reaction, the first being the infused one and the second from antibody formation. I have never seen the first stage of infused reaction in human beings. Second, I have seen 2 cases of longstanding sarcoidosis and additional terminal tuberculosis. In some way, both tuberculosis and sarcoidosis are related to the antigen-antibody reaction. In these 2 complex cases, the tissues react differently to the two agents; therefore, it is not only the antigen-antibody reaction which is involved. In sarcoidosis, there is a precipitation of hyaline masses without true scar formation. In general, antigen-antibody reactions are vascular reactions. In neither tuberculosis nor sarcoidosis are typical vascular reactions morphologically demonstrable.

DR. GERMUTH: I do not know how to answer that question because apparently I did not get all of it. The infused reaction, the one that I was talking about, of course, is a demonstration of the transfer of the serum sickness type by passive means.

DR. JAMES: It is unfortunate that at present we rely on human material as a source of Kveim antigen. I hope Merrill Chase will, in the future, provide sufficient active principle for worldwide epidemiologic surveys. We have examined various synthetic substitutes to see whether they can reproduce the Kveim test. The substances tested include Dr. Nina Choucroun's lipopolysaccharide (PmKo), mycolic acid and its ester, and pine pollen. Following an intradermal injection, the response to these substances was noted immediately, and at the end of twenty-four and forty-eight hours, and also in the course of a month. Any nodules observed at a month were biopsied and submitted blind to a pathologist, Dr. A. D. Thomson, who did not know whether the skin biopsy material was in response to conventional Kveim antigen, one of the substitutes, or from a naturally occurring cutaneous sarcoid lesion.

Lipopolysaccharide (PmKo) forms sarcoid nodules indistinguishable from those produced by Kveim antigen in Mantoux-positive normal subjects as well as in patients with tuberculosis and sarcoidosis. It is, therefore, nonspecific and valueless as a diagnostic test.

In 40 tests using pine pollen, a sarcoid nodule was produced once only, in a patient with erythema nodosum due to sarcoidosis. She had con-

tracted erythema nodosum during a holiday in pine-studded Bavaria.

DR. NELSON: What do you interpret from that?

DR. JAMES: So far, nothing. However, we must continue to look for alternatives to the present Kveim antigen if worldwide demand is to be met. A human source will always keep it in short supply.

DR. CHASE: Many years ago, Doan and Sabin injected into the skin of guinea pigs all sorts of chemical fractions made from tubercle bacilli. They made complex histologic observations after various periods of time and were able to show clearly the development of local granulomas around the site of deposition of various materials of the mycobacterial fractions.

DR. VOGEL: I would like to ask Dr. Chase if he tried to defat this fine material at all.

DR. CHASE: No. The problem stands in abeyance for want of time. But the presently described "whole" preparation has been designed to allow such studies. We do not intend to stop here. Nevertheless, I think that, with this particular spleen, one can work up portions repeatedly and obtain a uniform product to serve as standard.

Some other spleen sources also should give their "standard products," but their reactivities need not be identical with each other or with ours. The recommended "standard dose" in terms of dry weight might vary from one spleen to another.

DR. NELSON: Would the particle size be approximately the same?

DR. CHASE: Yes. There is no problem about controlling the particle size.

DR. NELSON: This is important; that is, if you believe in the Kveim reaction at all. At this point, we wish to discuss the current status of the Kveim reaction. If one asks Siltzbach, Chase, James, or Nelson, one gains a favorable impression of this test. On the other hand, Dr. Sones or Dr. Israel would probably have rather different ideas about it.

DR. ISRAEL: Dr. Chase's work is a giant step forward, and I hope it is going to eliminate the difficulties that we have had with crude extracts in the past, both those prepared for us by the late Dr. Joseph Aronson and those submitted by other investigators. Dr. Siltzbach has very properly emphasized that, if the Kveim test really becomes our diagnostic method, the burden will be shifted from the clinician to the pathologist. That is the point on which we have had some difficulty.

Having had our sections interpreted "blindly" by two university pathologists, we found considerable difficulty in getting them to agree on the line between the sarcoid tubercle and the nonspecific granuloma. So I would make just one plea: Before this test is regarded as clinically useful generally, it should be shown that not only expert pathologists, but also the average, competent pathologist, can make this distinction without repeating the test too often because of indefinite findings.

DR. NELSON: Dr. Hirsch, what do you think of the current status of the Kveim test?

DR. HIRSCH: I think I can answer at least some of Dr. Israel's objections or comments. Let me tell you what we did in the process of studying the 207 patients on whom Dr. Siltzbach reported. When we got into the sarcoidosis game five years ago, we decided that the question of the validity of the Kveim test was perhaps the most important one on the horizon. So we set as our first and major effort the solution of this problem. We had the benefit of expert assistance from many sources. Dr. Nelson provided us with antigen. Dr. Siltzbach provided us not only with good antigen but with his expert advice on how to do the test and how to interpret it.

Dr. Chase prepared and checked the antigens and also examined each patient repeatedly at the time of, and following, the injections. The biopsy slides were interpreted by Dr. John Ellis of New York Hospital, who had no knowledge of the clinical diagnosis on these patients. He made his diagnosis of a positive or negative Kveim reaction on the basis of the slides. Slides then went to Dr. Siltzbach, who also made a pathologic interpretation without knowledge of the clinical diagnosis. When it came time to analyze the cases—and this was done only last week—Dr. Siltzbach and I spent two days going over records. He saw the roentgenograms, clinical history, course, and tissue biopsy findings when they were available. The only thing unavailable to him was the result of the Kveim tests. On the basis of his clinical impression, the cases were divided into categories and, subsequently, the interpretation of the Kveim test by the two independent pathologists was added. The results showed convincingly that the Kveim test, when properly done with good antigen and when interpreted with understanding and with caution, is an extraordinarily good, specific test for sarcoidosis. As Dr. Siltzbach said, only 75 per cent of active patients give positive reactions, but this is true for many biologic tests, and especially for immunologic tests. I think this limitation is not severe, in terms of usefulness of the tests, for diagnosis and research.

Much more important, I think, is the fact that false positives are practically never encountered. Therefore, I predict the test will be very useful for eliminating the problem that Dr. Cummings alluded to, namely, that many of the patients in whom we have made a clinical diagnosis of sarcoidosis, on the basis of a roentgenogram and a biopsy, turn out at postmortem or at a later date

to have something entirely different, something unexpected.

Probably for lack of something better, we have come to rely too heavily on a tissue biopsy as supporting evidence for the diagnosis of sarcoidosis. On the basis of our experience at the present time, we place more reliance on the Kveim test than we do on a tissue biopsy. We have had several cases of histoplasmosis in our series. They have all been Kveim negative. We had one case of berylliosis, and the Kveim test was negative.

The point is, therefore, that in many of these other diseases which produce granulomas, pathologically indistinguishable from sarcoidosis, the Kveim test, properly applied, may permit one to separate this group and to study sarcoidosis. What I am proposing is that we might be better off using the Kveim test, properly done, as the primary diagnostic criterion for sarcoidosis. This might permit us to select a better group of patients for epidemiologic and other investigations.

I have just a word on another aspect. True, the Kveim test will be important for diagnosis when and if the antigen is widely available and when and if numerous investigators learn how to use it. But to me the real importance of the Kveim test is of a different nature. If this is a specific reaction associated with sarcoidosis, I think it holds the key, and the only good key we have now, to unlocking the door that hides the pathogenesis of sarcoidosis.

As Dr. Siltzbach showed, a positive Kveim test produces a lesion which is indistinguishable from the lesion which occurs naturally. The development of the Kveim test, time-wise and from the point of view of the pathology, is strikingly similar to the zirconium granuloma story told by Dr. Shelley. I should like to speculate on the possibility that the Kveim antigen contains the substance which is responsible for the sarcoidosis lesion. If the test is valid and meaningful, which we now believe it to be, studies in depth on the nature of the substance responsible for this activity should give us some real understanding of this disease.

DR. NELSON: Are there any other comments? We need about 6 pounds of spleen from a patient with sarcoidosis who has not received corticosteroids.

DR. ZIMMERMAN: I think the results presented by Dr. Siltzbach are very impressive, particularly the low incidence of false positives. However, I would like to ask a question relating to controls. This is a question that was touched on by Dr. Hirsch, but we need much more information. I think it is insufficient to say that included in the controls were patients with a variety of granulomatous diseases. We should be more specific. We have to get patients who not only have granulomatous disease but granulomatous diseases with a striking sarcoid-like reaction. This is the problem.

As Dr Siltzbach pointed out in his final conclusion, sarcoidosis is not a syndrome characterized by the way in which the reticuloendothelial system reacts, but, rather, a specific disease. To really get at this, it is necessary to have a number of cases, and these are difficult to find. We had some patients who originally had histoplasmosis with typical granulomatous reactions but who died a number of years later with sarcoidosis, pulmonary fibrosis, and insufficiency, and no demonstrable Histoplasma. Cases of this sort obviously are hard to find, but I think they are the type that should be studied.

One type that is fairly common, if you go to the right area, is tuberculoid leprosy. But I think we ought to have more information from Dr. Siltzbach of how many cases of this sort he had in his control series, and perhaps try to get at this type of patient for control.

DR. NELSON: Dr. Zimmerman, patients with tuberculoid leprosy have been tested with Kveim antigen in large numbers and are consistently negative. With a good antigen we almost never see a positive Kveim reaction in a leper, despite what you read from South Africa.

DR. ZIMMERMAN: The other disease I wanted to have information on was berylliosis.

DR. NELSON: I have had one patient with berylliosis who had a positive Kveim response.

Dr. HARDY: The few that we did in Boston were read by Dr. David Freiman as being foreign-body reactions.

DR. NELSON: I think it is very unusual to see a positive Kveim reaction in berylliosis.

DR. JAMES: Dr. Van Ostrand of Cleveland observed negative Kveim tests in beryllium disease. I have found them to be negative in leprosy, Hodgkin's disease, Crohn's disease, and in a variety of local sarcoid-tissue reactions.

DR. LONG: Some of us might have one of those 6-pound spleens. How do we tell if it is from a case of sarcoidosis? If the Kveim test is the best test for sarcoidosis, should we take a spleen from a man who has given the reaction?

DR. NELSON: This would be all right, but there are many ways other than the Kveim test that may be used to establish a diagnosis of sarcoidosis. Dr. Löfgren does not use the Kveim test.

DR. ANDERSON: I have reservations about the Kveim test as an epidemiologic tool if it gives 1 per cent false positives, and there is no other diagnostic test to screen out the false positives. If we take Nansemond County, Virginia, in which there were some 50 suspected cases of sarcoidosis, we would find about 40 positive Kveim reactions in this group, but 1 per cent false positives in the

total population of 38,000 would yield 380 positive Kveim reactions. As a result, it would not be possible really to know whether a positive reaction represented a clinical or false positive case without a second test.

DR. NELSON: Do you have any other biologic test that has a lower false positive index?

DR. SILTZBACH: Aren't Wasserman tests for syphilis performed there, and aren't they useful?

DR. ANDERSON: You have other means of ruling them out.

DR. SILTZBACH: In assessing the usefulness of the Kveim test as an epidemiologic tool in the face of its 2 per cent false positive results, one must also hold in mind that the present diagnostic methods used to detect sarcoidosis, which include clinical, roentgenographic, and histopathologic procedures, have a considerably higher level of diagnostic error. Indeed, I would suggest, and Dr. Cummings' follow-up autopsy reports indicate, that the error in diagnosis of sarcoidosis may reach 30 per cent. From a practical standpoint, what is actually done now is to Kveim-test those persons who, on mass survey chest films, show evidence of either hilar node enlargement or undiagnosed disseminated lung disease. It is in that group and in the symptomatic group that the Nickerson-Kveim test has proved itself especially useful.

In 1957, I made a survey of the literature, tabulating the results achieved by various investigators employing human sarcoid tissue suspensions as an intracutaneous Kveim-testing agent in sarcoidosis. I found then that false positive reactions were reported on an average of about 2 to 6 per cent among patients with diseases other than sarcoidosis or among persons with no demonstrable illness.

An exception to these findings was the Philadelphia experience of Drs. Israel, Sones, and their coworkers, in which false positive responses were encountered among 42 per cent of patients suffering from active tuberculosis. However, in a later report utilizing lymph nodes obtained from the same patient as a tissue source, no false positive reactions were encountered among tuberculous patients. In both series, less than 25 per cent of the patients with active sarcoidosis gave positive Kveim responses. Usually 75 per cent of patients with active sarcoidosis give positive reactions with satisfactory suspensions. This would indicate to me that the concentration of the specific active principle contained in the sarcoid lymph nodes used for the preparation of the Philadelphia testing suspensions was probably too low to be useful. Moreover, the frequent positive reactions obtained in the first series among the patients with tuberculosis would indicate that the nonspecific irritative qualities of their Kveim suspensions also made them unsuitable for use as testing agents in sarcoidosis.

I have had similar experiences and have had to reject as unsuitable almost half of the tissues used for making Kveim suspensions. Some tissue suspensions were inert, some were too weak in granuloma-inducing factor, and still others were unsuitable because they produced a confusing nonspecific foreign-body type of change among nonsarcoid subjects. Recently, Dr. Kooij of Capetown, South Africa, reported positive Kveim reactions in 3 patients with tuberculoid leprosy. He did not test patients with sarcoidosis. Earlier Dr. Wade had found no positive Kveim reactions among 10 patients with lepromatous leprosy.

Dr. Zimmerman asked about Kveim tests performed on patients with other granulomatous conditions. My experience with such patients is limited. We have tested more than 50 patients with tuberculosis of the usual variety, with one false positive Kveim response. I have also read tests on a single patient with histoplasmosis and on another with beryllium disease, both with negative responses. I have had 4 or 5 patients who showed evidence of a local sarcoid reaction in an excised lymph node which had drained a region involved with malignancy or chronic inflammatory disease. These patients failed to respond to the Kveim test as would be expected, since they did not have systemic sarcoidosis. Dr. James Hirsch had one patient with an enormous local granuloma of the lip. That patient had a negative Kveim reaction. I have tested a few patients with regional ileitis as well as with Hodgkin's disease, and I have not had a positive Kveim response in any of them. A few tests were performed utilizing a suspension made from a lymph node of a patient with regional ileitis. Neither the patient with ileitis nor a Kveim-positive patient with sarcoidosis responded.

DR. NELSON: Dr. Bernton, do you have any comments on Dr. Löfgren's tissue culture studies in sarcoidosis?

DR. BERNTON: Examination of granulomatous tissue in culture allows ample opportunity to study the natural history of the granuloma when removed from the body. Dr. Löfgren has shown us what is seen in this type of procedure. Certainly, at this time the significance of the PAS-positive granules, which Dr. Löfgren states are not specific, remains somewhat obscure. Perhaps it is wise to state that the type of migration noted here can also be seen in granulomas of other etiology. Tissue culture of the tuberculous lymph node shows first a lymphocytic phase of migration followed by macrophage migration. In the zones of macrophages, occasional giant cells may be seen. Eventually there is fibroblastic proliferation. The

granuloma of histoplasmosis, as derived from humans, behaves in much the same way. Perhaps our European colleagues are not faced with this problem, but one can unmask histoplasmosis in tissue culture. In my own experience, *Histoplasma capsulatum* (yeast phase) has been noted growing in the tissue culture preparation of lymph nodes derived from clinical cases.

In general, I think it can be stated that the tissue culture response of granulomas of sarcoidosis, tuberculosis, and histoplasmosis are morphologically quite similar.

DR. CHASE: Dr. Löfgren, I am not quite clear as to what happens in your tissue culture. Is it multiplication or transformation? In other words, do these little PAS-positive areas that you find in the cells actually divide along with cellular division, or is their number a reflection of previous experience of the same cell?

DR. LÖFGREN: The PAS-positive substance may of course exist in the original cells used for the tissue cultures. During the culturing, however, the substance appears in the new cells, first as small drops, then increasing and showing confluence to larger homogeneous masses, which in some cases include practically the entire protoplasm. In other words, the PAS-positive substance is most probably a result of a synthetic process, maybe of a degenerative nature.

SUMMARY

DAVID T. SMITH

The tissue cultures shown by Dr. Sven Löfgren fascinated me, but I question the concept that fibroblasts turn into large cells that go on to resemble giant cells. When I was a student in the tissue culture laboratory of Warren and Margaret Lewis, I learned several things about monocytes. Monocytes often spread out into long filaments that were at times indistinguishable from fibroblasts. They were phagocytic and ate up the dead lymphocytes and other fragments of cells, changed their shape, developed the kind of nucleus shown in the illustrations and also numerous cytoplasmic granules. While it is presumptuous of me to look at these pictures and say they are not modified fibroblasts, at least I would raise a question as to whether they are, in effect, modified monocytes or histocytes, which are always present in tissues. I think it is extremely important to study these cells in tissue culture.

Dr. Siltzbach has about persuaded me that this Nickerson-Kveim test or just the Kveim test is important. I have been one of the doubters, although I have not worked at the problem myself. When you can begin with a large active spleen and can get a standardized method of preparation as Dr. Chase has done, then it is not necessary that each spleen have originally the same amount of the active principle.

Dr. Koch made himself up a soup and said "This is Old Tuberculin," which in certain doses will give certain specific reactions. Now, if you want a new batch of tuberculin, you make it and standardize it against the old. Then you write a paper and the man investigating in Germany or in France knows pretty well what you are doing. This is the first chance, as I see it, of getting the Kveim test standardized against the original material, and then results would certainly become comparable. I hope someone will use this in Europe. I see that it has been used in Florida, but has it been used in Europe?

DR. SILTZBACH: Yes.

DR. SMITH: And does it work in Europe?

DR. SILTZBACH: Just a few times in England. Did you mean my material?

DR. SMITH: Yes.

DR. SILTZBACH: Just a few times in England, and it worked there. I have not sent it abroad.

DR. SMITH: We are trying to see if we have the same sarcoidosis in Europe as in this country. This would be one of the tests.

DR. JAMES: Let us resolve all doubts about that. Sarcoidosis is the same, and the antigens and the Kveim test work in Europe.

DR. SMITH: Dr. Chase's work I have already alluded to in connection with Dr. Siltzbach. This is absolutely basic and will result in standardization that will really facilitate progress.

Dr. Germuth has a fascinating study in classical immunology. I have never seen a more beautiful one. I am impressed, however, with the statement he made in his discussion—and I hope he will correct me if I misinterpreted it—that he did not get granulomas if he excluded complement from the animals. Was that done by an anticomplement antibody?

DR. GERMUTH: That was done by absorbing it out.

DR. SMITH: If you do not get the granulomas in the absence of complement, it would seem to me that your total granuloma is reacting and ultimately depends upon microscopic necrosis or microscopic Arthus phenomenon with tissue damage. It is the dead tissue then which sets up your mechanical basis for the monocytes and the giant cells, which pleased me very much because it produces the

kind of thing you have shown so beautifully, as a manifestation of classical antibody reaction.

I think this kind of result in classical antibody reaction has been ignored in the past. Certainly, the lesions of this kind in the sulfonamide sensitivity resulted in the death of the patient. Other chemical changes all fit in with antigen-antibody, but antigen and antibody of the classical type, the precipitating type, in contrast to the tuberculin type of antibody reaction.

Dr. Vogel's beautiful paper and the discussion that went with it are very illuminating.

I am not very excited about 40mμ particles or 10-mμ particles. I do not know whether 40mμ particles can be breathed all the way down under natural conditions or not. But I will confirm Dr. Michael's statement that, when the pine trees are really very active, they simply cover the ground with pollen. I was in Saranac when Dr. Gardner succeeded in producing typical silicosis in guinea pigs and rabbits when all investigators had previously failed. In order to do so, he had to expose the animals for eight hours a day, up to a year, to silica particles which were so thick you could hardly see through them. So only an extremely minute fraction of the silica that went into the nasal passages ever got into the lungs, but eventually there was enough to produce typical silicosis.

I am interested, too, in the possibility that Dr. Vogel is getting two kinds of antibody reactions. The development of anaphylaxis depends upon the presence of classical humoral antibodies. But he has acid-fast material combined with protein which can give the tuberculin type of reaction. So I think he has a combination of the classical antibody and the tuberculin type of antibody. Of course, as a matter of fact, there is a small amount of classical antibody reaction in tuberculosis, easily demonstrated in the rabbit but with more difficulty in man.

I would like to call to your attention the possible significance of ingestion of pine pollen. I am thinking, of course, of the work that Dr. Felton did in which he found that carrots, cabbage, and cauliflower had polysaccharides which were the same chemically as some of the pneumococcal polysaccharides, so that people could eat these vegetables and make specific antibodies without having contact with the specific type of pneumococcus. More important is the fact that these polysaccharides are stored in the body, since we have no natural mechanism for destroying them. They could be stored in the body from vegetable material that was taken in as food. One might eat pine pollen (even if the big particles cannot be breathed in) and store some of its antigenic components in his lymph nodes. Then only the unlucky person who would happen to have the kind of constitution that would allow him to become sensitized would react. I am not yet convinced that pine pollen is the cause of sarcoidosis. I am simply trying to say it has not been eliminated and that ingestion is a mechanism that should be considered before we say that the pine pollen theory has been disproved.

I think Dr. Ungar laid the foundation very well for the subsequent papers. He showed that the true tuberculin type of allergy, with its granulation tissue and necrosis, is an essential part of the reaction. With long-chain fatty acids he obtained the colloid type of giant cell. Apparently there must be some tissue damage from the long-chain fatty acid before the formation of granulation tissue which might be mistaken for sarcoid. But these reactions are not sarcoid as defined and discussed in this symposium.

ANALYSIS OF INCIDENCE AND MORTALITY DATA IN THE UNITED STATES

THOMAS D. DUBLIN, *Moderator*

INTRODUCTION

DR. DUBLIN: Our agenda for the balance of this morning's session is to consider a limited, or rather a segmental, aspect of the epidemiology of this increasingly important and now better recognized condition, sarcoidosis. I use the term "segmental aspect" because the two measurements to be considered, namely, incidence and mortality, provide only a partial picture of the distribution of a disease in a population, and offer only a tentative clue to the factors that influence the selection of certain individuals by the disease.

As we shall see from the formal presentations and the general discussion to follow, even these two epidemiologic indicators are as yet subject to wide variations due as much to the differences in degree to which sarcoidosis is recognized and reported as a cause of illness or death as to the true differences of selection of one population against another. I believe it can be stated, however, that, as the medical profession becomes better acquainted with the disease and is better able to recognize the wide range of clinical manifestations and severity that are encompassed by this condition, our epidemiologic knowledge will also be enhanced. There is little question in my mind that major improvements in our understanding of sarcoidosis have occurred in the last few years and further advances are bound to come in the years ahead. Perhaps at that time we also shall have access to other useful epidemiologic indicators, including, for example, true incidence rates (as opposed to discovery rates), prevalence, secondary attack rates, survival rates (or their counterparts, case fatality rates), and perhaps others. Also, it is hoped that our information will not be limited to small segments of our population—for example, members of the Armed Forces—and that it will be reasonably possible to compare the distribution of the disease from one country to another or between different geographic areas.

For the present, however, we are forced to limit our attention to the relatively few studies that are available, and we are indeed grateful to Colonel Cooch, Commander Gundelfinger, and Captain Britten, Dr. Moriyama, Dr. Abeles, and their associates, who have compiled and analyzed data available to them for presentation today. Perhaps their efforts will stimulate and encourage others to shed much-needed light on the selective distribution of sarcoidosis in other population groups.

May I now call on Lieutenant Colonel Joseph W. Cooch to report on sarcoidosis in the United States Army, 1952 through 1956.

SARCOIDOSIS IN THE UNITED STATES ARMY, 1952 THROUGH 1956[1]

JOSEPH W. COOCH

INTRODUCTION

It is not the purpose of this report to review the previous epidemiologic studies reported concerning the occurrence of sarcoidosis in military personnel and veterans. The study was designed, rather, to add to the body of data available, and consisted of a review of a comparatively large group of records of United States Army personnel with sarcoidosis.

[1] From the Preventive Medicine Division, Communicable Disease Branch, Office of the Surgeon General, Department of the Army, Room 2521, Main Navy Building, Washington, D. C.

METHODS AND MATERIALS

Among the machine records' punch cards that were prepared for cases closed in Army hospitals during the years 1953 through 1956, there were 462 representing cases of sarcoidosis. The cards are a mixed sample, consisting of all the records for cases resulting in disability or death, with various percentages for the different outcomes. There were, of course, some duplications.

Requests were made for the personnel records of the patients for whom the punch cards had been prepared. A total of 400 cases was available for study.

The cases were reviewed and the following data, when available, were recorded: name, Army service number, rank, race, date of admission to the

TABLE 31

ADMISSION RATES AND INCIDENCE RATES OF SARCOIDOSIS IN THE U. S. ARMY, WORLDWIDE, 1952 THROUGH 1956

	New Admissions*		Incidence†	
Year	Cases	Rates‡	Cases	Rates‡
1952	120	7	135	8
1953	175	11	175	11
1954	100	7	105	7
1955	134	11	164	14
1956	147	14	169	16
Mean		10		11

* To hospital or quarters in an excused-from-duty status.

† Consists of all new diagnoses of sarcoidosis—both cause of admission and cases secondary to some other cause of admission.

‡ All rates are the number per 100,000 mean strength per year.

TABLE 32

RELATIONSHIP OF AGE TO CASE RATIOS OF SARCOIDOSIS

Age Group	Cases	Ratio per 100,000*
years		
Less than 20	16	11.4
20 to 24	179	22.5
25 to 29	56	30.1
30 to 34	16	16.7
35 and older	16	11.7
Not recorded	8	

* For the five-year period, 1952 through 1956.

TABLE 33

SARCOIDOSIS RELATED TO LENGTH OF SERVICE

Length of Service	Cases	Ratios per 100,000*
Less than 1 year	34	8.5
1 but less than 2 years	120	28.1
2 but less than 3 years	38	36.2
3 but less than 5 years	33	35.3
5 but less than 8 years	23	22.1
8 but less than 20 years	33	15.5
20 years and more	1	6.9
Not recorded	9	

* For the five-year period, 1952 through 1956.

hospital, age on admission, length of service, state of birth, diagnosis, basis upon which the diagnosis was reached, and the disposition.

A number of the punch cards represented duplicate hospital admissions of the same person. For other patients no record was available at all, and in still others the record was too fragmentary to permit an evaluation. There were, however, 353 records of patients in whom a diagnosis of sarcoidosis had been made. Of these, 291 contained a pathologic report stating, at the least, that a tissue specimen "showed lesions compatible with sarcoidosis." The following observations were based on study of the latter 291 cases.

Population analyses were obtained as follows: The statistical section of the Office of the Adjutant General maintains a record of the total number of persons in each military grade daily. Upon request, this office furnished the number of persons in each grade for each of the years, 1952 through 1956, as of June 30 of each year. The data included the respective numbers of Negroes and whites in each grade.

Population distributions by age and length of service were obtained from the records of the Sample Survey of Military Personnel conducted periodically by the Adjutant General. Although these data are based on a 5 per cent sample rather than on complete population records, it is believed that they are truly representative.

The cases reviewed and accepted as having confirmed diagnoses of sarcoidosis were then compared to the various population breakdowns. While it is apparent that the relationships derived do not represent true "incidence," that term will be used in this report to represent the ratio of the number of cases to the mean population throughout the period, unless otherwise specified in the text. The "incidences" are comparable in any one tabulation, but usually they are not comparable between one tabulation and another.

RESULTS

The reported incidence of sarcoidosis for Army active-duty personnel for the years 1952 through 1956, showing the trend in reported incidence, is shown in table 31. This table is based upon all reported cases, rather than on the selected cases.

The ratio of the 291 selected cases by age groups is shown in table 32. While the greatest number of cases occurred in patients aged twenty through twenty-four, this age group represented the greatest population at risk. The highest ratio was in the twenty-five– to twenty-nine–year age group.

The ratios based on length of service are shown in table 33. The ratios do not vary significantly with length of service. On the other hand, the greatest number of cases occurred in the second year of service. Among active-duty personnel admitted for sarcoidosis, 42 per cent had had between one and two years of service at the time of admission.

One factor which led to the diagnosis during this period was the fact that toward the end of the second year, as a part of the preseparation physical examination, a chest roentgenogram was (and still is) made on all two-year inductees. The observation of abnormal findings in the film led to further study and, eventually, to the diagnosis of sarcoidosis. Many of these patients had no symptoms at the time their lesions were discovered.

The relative ratios according to rank may be seen in table 34. Since the standard deviation of these data is 8.1 and the mean rate is 18.6, it is apparent that with one exception all values lie within two standard deviations of the mean, and there is little or no relationship of the incidence to rank. The exception is the low rate for commissioned officers, an observation which could be accounted for by the selection system, which submits officer candidates to a more rigorous physical examination than it does recruits.

The comparative ratios of cases in Negro and non-Negro personnel are shown ie table 35. The non-Negro population at risk includes a small number of non-Caucasians, and one of the present patients was a non-Caucasian (an American Indian). However, it is not believed that, even if it had been possible to exclude all non-Caucasians from the numerator and denominator of the non-Negroes, the difference from Negro ratios would have been substantially altered. While there are some internal differences from year to year, differences between Negro and non-Negro far outweigh the internal differences. The probability that the difference observed was a chance one is far beyond any scale available.

As population data for the area of birth of Army active-duty personnel are not available, another source of comparable population breakdown had to be sought. This was found in table 29 of *Statistical Abstracts of the United States* (1), which lists the population by race and sex, according to the state of residence in 1950. While it cannot be assumed that the state of birth of the military population is completely proportional to the population breakdown used, the differences are not believed to be great. With the possible error in mind, however, observation of table 36 will reveal that the rates in the East-Southcentral states (Kentucky, Tennessee, Alabama, and Mississippi) are substantially higher than those in any other region of the United States. Even the rate for white persons is higher in this area than in any other region. The high rate for the Negro population for the Northeast region is a matter of sample size, since only 2 cases are involved. In the West-Northcentral group, 6 of the 7 patients were born in Missouri. On the other hand, the South Atlantic region (Delaware, Maryland, D. C., Virginia, North Carolina, Georgia, and Florida) had

TABLE 34

SARCOIDOSIS RELATED TO RANK

Rank	Cases	Ratios per 100,000 Male Personnel*
Officers	13	10.1
E-7	6	12.8
E-6	16	20.0
E-5	37	28.1
E-4	61	27.2
E-3	80	26.1
E-2	54	19.7
E-1	7	4.7
Not recorded	14	

* For the five-year period, 1952 through 1956.

TABLE 35

SARCOIDOSIS RATIOS BY RACE

Year	Negro	Non-Negro	Total	Ratio Negro/Non-Negro
1952	127.3	2.8	18.2	45/1
1953	209.9	10.5	36.6	20/1
1954	278.5	13.0	45.6	21/1
1955	405.5	29.3	74.4	14/1
1956	266.6	26.7	50.8	10/1
Mean	247.1	15.5	44.2	16/1

TABLE 36

SARCOIDOSIS RATIOS RELATED TO AREA OF BIRTH AS COMPARED BETWEEN RACES

Ratios*

Region	White	Negro	Total
Northeast	0.5	28.1	1.0
Middle Atlantic	0.9	4.5	1.1
East-Northcentral	1.1	7.9	1.3
West-Northcentral	1.2	33.8	2.2
South Atlantic	2.6	35.9	10.6
East-Southcentral	3.5	45.3	26.7
West-Southcentral	1.9	21.2	5.1
Mountain	0	0	0
Pacific	0.2	8.7	1.1

* Expressed in cases occurring during the study per million individuals enumerated in the 1950 census.

TABLE 37

SARCOIDOSIS RATIOS IN ARMY PERSONNEL BORN IN SOUTHEASTERN UNITED STATES COMPARED WITH REST OF THE UNITED STATES

	Rate*		
	Native White	Negro	Total
Southeastern United States†	3.8	41.5	13.2
Rest of United States	0.7	8.8	1.2
Total United States	1.3	26.7	4.0

* Expressed in cases occurring during the study per million individuals enumerated in the 1950 census.

† Virginia, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, Arkansas, Tennessee, and Missouri.

more Negro cases (89) than the East-Southcentral region (59).

The following states as a group were designated the southeastern part of the United States: Virginia, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Louisiana, Arkansas, Tennessee, and Missouri. This area then was compared with the remainder of the United States, and the rates are tabulated in table 37, using these populations. The ratio of Negro to white rates is 21 to 1, and the ratio of incidence in the southeastern United States to that in the rest of the country is 11 to 1.

The location of the birthplaces of the individuals is likewise shown on the map (figure 47), in which the exact location is spotted as accurately as possible. This map excludes 2 patients (one from Michigan and one from Mississippi) for whom the postal guide and available atlases list no such town as was given. Also excluded are 4 patients who were born in Puerto Rico; one each who were born in Algiers, British Honduras, and Germany; as well as 8 patients for whom no birthplace was recorded.

When the place of birth was identified, the population during the 1950 census was determined. It was observed that 141 patients were born in communities classified as urban, i.e., communities of 2,500 or more (2), and 135 were from rural areas. Applying the urban and rural populations in 1950, a ratio of 1.6 cases per million persons was observed for urban populations, and 2.2 cases per million persons for rural populations. Although these differences are of borderline significance, it must be remembered that, on the one hand, all of the individuals were also included in the 1940 census when many of the communities from which they came were smaller. On the other hand, the proportion of urban to rural population increased somewhat from 1940 to 1950 (3). Unfortunately, the 1940 populations for the places of birth were not available at the time this paper was prepared.

DISCUSSION

It is apparent that these data do not show true incidence rates for sarcoidosis in the United States Army. Even table 31, which shows the number of cases and rates for admission and incidence, is based on diagnoses of various degrees of precision. The other data represent a selected group of patients: those whose records were available and in whom the diagnosis was supported by a pathologic report. It is believed, however, that they are representative of the relative incidence of sarcoidosis in the various populations at risk among military personnel and that, within the group, comparisons may be made with confidence.

The populations at risk are based partly on 100 per cent samples, partly on 5 per cent samples, and partly on comparable population groups counted in the 1950 census. While allowances must be made for strict noncomparability, it is believed that the errors are randomized and that these data, too, are representative.

No reason is apparent for the increased reporting of sarcoidosis after 1952, but an increased awareness of the condition is believed to be responsible for the increased number of diagnoses.

There is no evidence from the data that among military personnel there is any age at which the disease is most likely to occur. As previously mentioned, cases were discovered predominantly during the second year of service, but rates for various lengths of service were variable, without any detectable trend. This factor also has its effect in the age distribution.

There does appear to be a slight relation to rank in that commissioned officers have a lower incidence, but the difference is of borderline significance.

The relationship to race is apparent, as is the relationship to state of birth. These two factors are, of course, interrelated, and which factor has the greatest effect on the other cannot be decided from these data. The apparently greater incidence

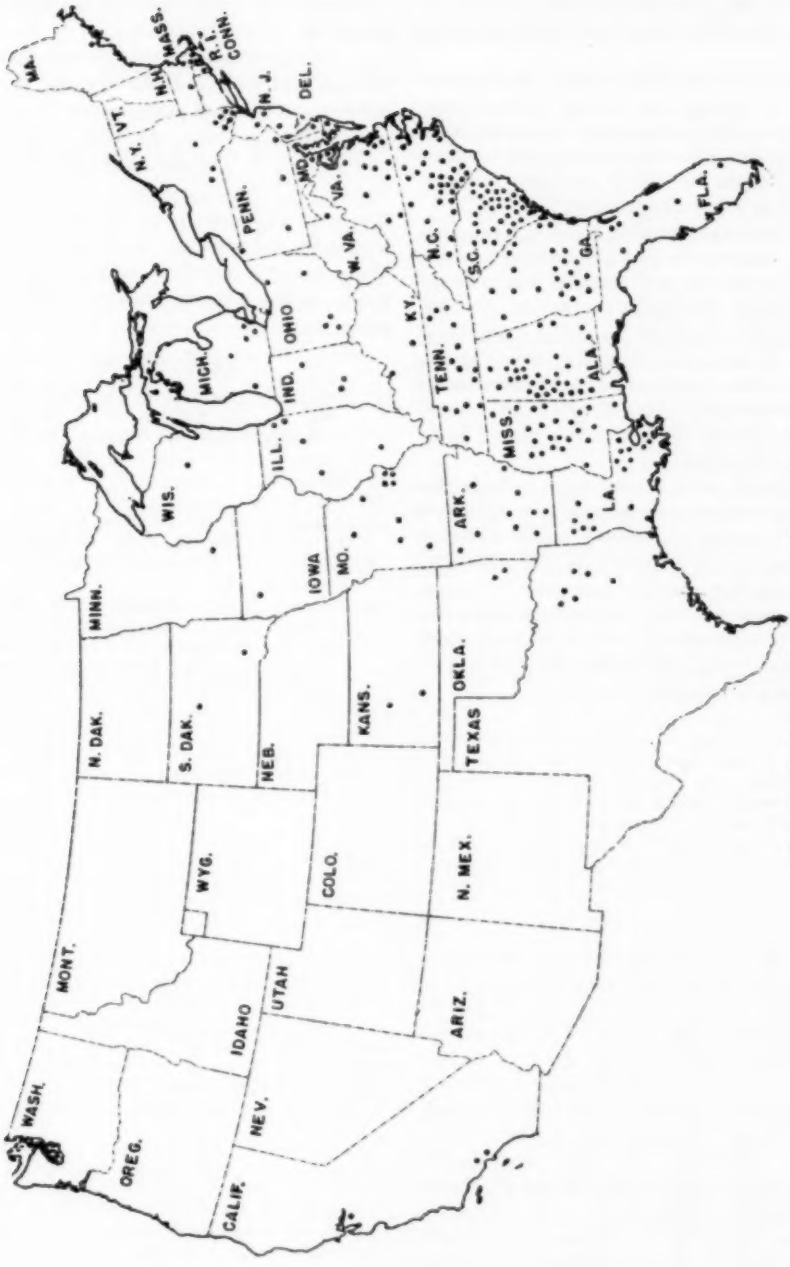

FIG. 47. Birthplaces of patients with sarcoidosis.

in those whose places of birth were rural as opposed to urban is likewise related to the other two factors.

The map and data pertaining to place of birth confirm, in general, the finding of others who have studied the epidemiology of sarcoidosis in the United States, but it is not any easier to draw firm conclusions with these new data added to the old than it was without them.

The observations confirm those of Cummings and his associates (4) that the birthplaces of the patients are related to the nonarid section of the United States. The comparison of case distribution to areas of pine forest, also suggested by these authors, is less apparent in the current study. There is a closer relation to the distribution of red-yellow soils, as suggested by Gentry, Nitowsky, and Michael (5), but in this respect many cases are exceptions.

The place of birth is not always an indication of the place of greatest exposure. In a population which is becoming progressively mobile with each decade, any individual may have been exposed to circumstances in many different areas. It has not, however, been possible to find enough data in the records to establish any sort of life-table study which would take into account the various areas where persons have lived.

The only firm conclusions that can be made are as follows:

(*a*) In United States Army personnel from 1952 through 1956, sarcoidosis was most apt to be discovered as a result of preseparation chest roentgenograms taken during the second year of military service. (*b*) The disease occurs much more frequently in Negroes than in non-Negroes. (*c*) It occurs with much greater frequency in persons born in the southeastern United States than elsewhere. (*d*) It is a little more likely to occur in persons whose birthplace was rural rather than urban.

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SARCOIDOSIS IN THE UNITED STATES NAVY[1,2]

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INTRODUCTION

Epidemiologic observations on sarcoidosis occurring in United States military veterans have demonstrated concentrations of cases, based upon place of birth, in the southeastern portion of the country, as well as a significant accumulation of cases in the New England and North Central states (1–3). These findings indicate that sarcoidosis may be a disease associated with certain geographic areas, and that environmental factors peculiar to these regions may be of etiologic importance in the development of the disease.

Military populations are well suited to some types of epidemiologic studies because many of their attributes are reasonably well known and subject to control. Sarcoidosis is reported with sufficient frequency in naval personnel to provide opportunity for many types of studies. The present paper is concerned with developing some of the epidemiologic features of sarcoidosis as observed in the United States Navy in recent years.

MATERIAL AND METHODS

The data for this report were obtained from statistical reports of sarcoid patients submitted to the Bureau of Medicine and Surgery, Navy Department, during the years 1954 through 1958. The date of initial hospitalization leading to the diagnosis of sarcoidosis was taken as the time of onset. Incidence rates were computed on the basis of the data of total military strength furnished by the Bureau of Naval Personnel. Except as mentioned below, readmissions with sarcoidosis were excluded from computations. A total of 303 cases were reported.

Data on the distribution of naval personnel by race have not been available since 1952. Therefore, it was necessary to estimate the racial composition of the population by assuming that the 1952 age distribution for Negro and other races remained constant throughout subsequent years and that the change in racial composition between 1952 and 1959, when a special analysis was made, was linear.

In addition to the statistical reports of patients, the medical records of sarcoid patients hospitalized during 1957 and 1958 were studied to determine criteria for diagnosis, place of birth, place of residence at time of entry into the service, and status of the tuberculin reaction. Many of these cases were initially diagnosed in previous years, so that the data from this part of the study are more related to prevalence than incidence. A total of 132 cases was so analyzed. Since practical considerations required the selection of this sample on the basis of hospitalization during these two years, it is not necessarily representative of the entire group of sarcoid patients studied. The age and length of service characteristics of the selected group of 132 patients were essentially the same as for the total group of 303 patients. However, the selected group contains a higher proportion of Negro patients than does the entire group.

The diagnosis of sarcoidosis was accepted in each case. The information contained in the medical records on file in the Bureau was not sufficiently detailed to permit a critical appraisal of individual diagnoses. In general, the diagnosis was based on the clinical, roentgenographic, and laboratory findings, the exclusion of tuberculous and fungal infections by cultural techniques, and the results of biopsy examination. A positive biopsy was usually indicated in the medical record by the statement "compatible with sarcoidosis." Of the 132 patients reviewed, a biopsy was performed in 125, all but 13 of which were reported positive. There was no record of a biopsy in 7 patients. The scalene lymph nodes were the tissues most frequently biopsied. Paratracheal and liver biopsies were also performed. Of importance to this study is the observation that the great majority of the patients were detected as a result of a routine physical examination which included a roentgenographic examination of the chest.

RESULTS

The incidence of sarcoidosis in the Navy and Marine Corps for the 10-year period 1949 through 1958 is shown in table 38. The rising incidence seen through 1956 may be due to an increased awareness of the disease and to the more frequent use of biopsy examination.

Rank and race: The incidence of sarcoidosis in various types of naval personnel during the years 1954 and 1958 is listed in table 39. There was no difference in the frequency of the occurrence of sarcoidosis in Navy and Marine Corps personnel. Differences between the military environments of these two services apparently do not affect the incidence of sarcoidosis.

The difference observed between the incidence

[1] From the Bureau of Medicine and Surgery, Department of the Navy, Washington, D. C.

[2] The opinions and assertions expressed herein are those of the writers, and are not to be construed as reflecting the views of the Navy Department or the naval service at large.

TABLE 38

INCIDENCE OF SARCOIDOSIS IN THE UNITED STATES NAVY AND MARINE CORPS, 1949 THROUGH 1958

Year	Number of Cases	Rate per 100,000 per Annum
1949	11	2.1
1950	14	2.6
1951	31	3.4
1952	37	3.5
1953	42	4.0
1954	55	5.7
1955	62	7.0
1956	74	8.4
1957	63	7.2
1958	49	5.8
Total	438	5.1

TABLE 39

INCIDENCE OF SARCOIDOSIS, BY TYPE OF PERSONNEL, IN THE UNITED STATES NAVY AND MARINE CORPS, 1954 THROUGH 1958

Type of Personnel	Number of Cases	Incidence Rate per 100,000 per Annum
Navy	231	6.8
Marine Corps	72	6.9
Officer	45	9.7
Enlisted	258	6.5
White*	212	5.0
Negro	91	47.8
Male	296	6.7
Female	7	13.3
Total	303	6.8

* Includes 1 Mongolian and 3 Malayans.

rates among officers and enlisted personnel is highly significant statistically. There is no ready explanation for this difference in the data on hand. There were no cases among Negro officers, whose strength is unknown.

The incidence rate among Negroes was almost ten times that observed among whites. The relatively high incidence rate among females was based on 7 cases and is not statistically significant.

Age: The ages of the sarcoid patients ranged from seventeen to forty-nine years. The median age was twenty-nine years for officers, twenty-three years for the enlisted white patients, and twenty-two years for the Negro patients.

The age-specific attack rates for various population subgroups are shown in table 40. It is apparent that the Negro age-specific attack rates are considerably higher than the rates for whites. The rates for officers are higher than those of the white enlisted personnel for all age groups except the forty- to forty-four-year group. There was an average of only 16 officers in the age group of seventeen to nineteen during the period 1954 through 1958, so that the absence of sarcoidosis in this age group may be expected. The peak attack rate for enlisted personnel, both Negro and white, occurred in the age group of twenty to twenty-four years. Among officers, the maximal attack rate occurred five years later, in the twenty-five- to twenty-nine-year age group. Of possible significance is the apparent tendency of the rates to increase in the older age groups in all patients.

Length of service: The length of service of the sarcoid patients ranged from less than three months to twenty-five years. The median length of service for the officers was 9.2 years, for the enlisted whites 3.6 years, and for the enlisted Negroes 2.0 years.

The incidence and annual incidence rates of sarcoidosis based upon length of service are listed in table 41.

Information on the racial composition of the population by length of service was not available. The attack rates among officers were generally

TABLE 40

INCIDENCE OF SARCOIDOSIS BY AGE GROUP, RANK, AND RACE, UNITED STATES NAVY AND MARINE CORPS, 1954 THROUGH 1958

Age Group	Number of Cases				Rate per 100,000 per Annum			
	Total	Officers	Enlisted Personnel		Total	Officers	Enlisted Personnel	
			White*	Negro			White	Negro
years								
17–19	28	—	15	13	2.5	—	1.4	32.3
20–24	171	8	107	56	9.2	7.3	6.4	71.6
25–29	48	15	25	8	8.4	14.7	5.9	18.6
30–34	31	11	11	9	7.1	13.8	3.2	54.0
35–39	17	7	6	4	5.8	8.2	3.1	39.4
40–44	5	1	3	1	4.5	2.0	5.1	53.0
45–49	3	3	—	—	7.2	11.7	—	—
Total	303	45	167	91	6.8	9.7	4.4	47.8

* Includes 1 Mongolian and 3 Malayan cases.

higher than those among enlisted personnel. Maximal attack rates occurred among officers who served from eight to fourteen years; the maximal rates among enlisted personnel occurred during the second to eighth year of service. An examination of the data for the number of officers will show an irregular distribution in terms of length of service. Officer strength declined after four years of service to a low in the tenth to twelfth year; it then reached a maximal peak in the fourteenth to sixteenth year, after which there was again a decline. Enlisted strength, on the other hand, dropped quite precipitously by the fourth year of service, and declined fairly uniformly thereafter. The effect of these changes in personnel strength on the observed incidence of sarcoidosis will be considered later.

Residence: The medical records of all patients hospitalized because of sarcoidosis during the years 1957 and 1958 were studied to determine birthplace and place of residence at the time of entry into naval service. Several of these patients had been hospitalized with sarcoidosis in previous years, so that these cases are related to the prevalence of disease during these two years. A total of 132 records was studied.

The geographic distribution of the sarcoid patients by place of birth and residence is shown in table 42. No information was available as to length of residence in a given state at the time of entry into the service. Correlating birthplace with residence might be used as a first approximation for estimating the duration of exposure in the area of residence. The number of patients whose birthplaces and residences were in the same state or region may also be seen in table 42. It appears that most of the patients residing in the eastern, southern, and central states were also born in those states. In contrast, only 4 of the 14 patients residing in the Pacific states were natives of those states. Of the remaining 10, only 2 were born in a state which had a fairly high sarcoidosis rate (Louisiana). It was not possible to compute attack rates by place of birth since the distribution of naval personnel by birthplace is unknown.

The racial distribution of the sarcoid patients by place of residence is shown in table 43. The data for individual states have been combined into geographic divisions, and only those states with proportionately large numbers of cases are shown individually. The statistical significance of the observed rates is indicated. A probability level of less than 0.05 as determined by the chi-square method was considered significant. The number of Negro personnel residing in most of the areas listed was too small to permit statistical analysis. This was also true of most individual states, even when the personnel of both races was combined. The small numbers also precluded testing the significance of the observed differences between races in any state or region. The difference in attack rates between the two races for the entire population is highly significant statistically.

The attack rates for both races are higher than expected for persons residing in the South Atlantic and East-Southcentral divisions, and lower than expected in the East-Northcentral division and in California. The low rate observed among residents of the Mountain division approaches statistical significance ($chi^2 = 3.56$). For whites residing in the state of Pennsylvania and the South Atlantic division, the rates are higher than expected on the basis of the average rate for whites. The white rate is significantly lower than expected among residents of California. The East-Southcentral division had an unusually high race-specific rate among Negroes residing there. The lack of statistical significance of the Negro rates for the South Atlantic and West-Southcentral divisions may be explained by the fact that most of the personnel of this race reside in the South Atlantic and South Central regions. The combined Negro rate for the New England, Middle Atlantic,

TABLE 41

INCIDENCE OF SARCOIDOSIS BY LENGTH OF SERVICE* AND RANK, UNITED STATES NAVY AND MARINE CORPS, 1954 THROUGH 1958

Length of Service	Number of Cases			Rate per 100,000 per Annum		
	Total	Officers	Enlisted Personnel	Total	Officers	Enlisted Personnel
years						
0–1	54	8	46	3.5	18.0	3.1
2–3	116	10	106	10.5	18.2	10.1
4–5	53	—	53	15.7	—	18.8
6–7	17	2	15	11.3	7.2	12.1
8–9	9	4	5	4.5	22.8	2.7
10–11	16	5	11	8.9	38.0	6.6
12–13	15	4	11	7.3	19.2	6.0
14–15	9	6	3	3.7	8.0	1.8
16–25	14	6	8	4.4	5.7	3.7
Total	303	45	258	6.8	9.7	6.5

* Includes service creditable for pay purposes.

TABLE 42

INCIDENCE OF SARCOIDOSIS BY PLACE OF RESIDENCE AND BIRTH, UNITED STATES NAVY AND MARINE CORPS, 1954 THROUGH 1958

State	Number of Cases			State	Number of Cases		
	Residence	Birthplace	Residence and Birthplace		Residence	Birthplace	Residence and Birthplace
New England	7	8	5	West-Northcentral	6	6	4
Maine				Minnesota	1	1	
New Hampshire				Iowa	1		
Vermont				Missouri	3	2	2
Massachusetts	6	7	5	North Dakota			
Rhode Island		1		South Dakota		1	
Connecticut	1			Nebraska			
				Kansas	1	2	1
Middle Atlantic	21	21	17	West-Southcentral	12	17	12
New York	9	10	7	Arkansas		1	
New Jersey	1	2		Louisiana	7	10	7
Pennsylvania	11	9	9	Oklahoma	1	1	1
				Texas	4	5	3
South Atlantic	42	40	37	Mountain	1	2	1
Delaware				Montana		1	
Maryland	1			Idaho			
District of Columbia	1			Wyoming			
Virginia	4	4	4	Colorado	1	1	1
West Virginia	4	4	3	New Mexico			
North Carolina	10	10	8	Arizona			
South Carolina	10	10	9	Utah			
Georgia	6	9	6	Nevada			
Florida	6	3	3				
East-Northcentral	9	9	6	Pacific	14	7	4
Ohio	5	3	3	Washington	7	2	1
Indiana	1	1	1	Oregon	2	1	1
Illinois	1	1		California	5	4	1
Michigan							
Wisconsin	2	4	2	Unknown	4	3	2
East-Southcentral	16	18	15	Other (Chile)		1	
Kentucky		1					
Tennessee	7	6	6				
Alabama	3	3	2				
Mississippi	6	8	6	Total	132	132	103 92

North Central, Mountain, and Pacific states is significantly lower than expected.

The rates observed for several individual states are of interest. Personnel of both races residing in North and South Carolina appeared to have higher-than-average sarcoidosis rates. The highest rate was observed among Negroes residing in Mississippi. The highest rate observed for whites occurred among those residing in the state of Washington. Only one of the 7 white sarcoid patients residing in Washington was also born there. The remaining 6 patients were born in New Jersey, Illinois, Minnesota, Kansas, Texas, and Montana; none of these states is particularly notable for prevalence of sarcoidosis. One other patient was born in Washington, but his residence at the time of entry into the service is unknown.

Unfortunately, the residence of 4 of the patients could not be determined. It also was not possible to determine the attack rates for officers by place of residence, since information on residence of officer personnel was not available

TABLE 43

INCIDENCE OF SARCOIDOSIS BY RESIDENCE AND RACE, UNITED STATES NAVY AND MARINE CORPS, 1957 THROUGH 1958

Residence	Number of Cases			Rate per 100,000 per Annum		
	Total	White	Negro	Total	White	Negro
New England	7	7	0	6.9*	7.1*	—
Massachusetts	6	6	0	12.2	12.4*	—
Middle Atlantic	21	19	2	8.9*	8.5*	15.2*
New York	9	7	2	8.9*	7.3*	33.9
Pennsylvania	11	11	0	11.5*	12.2†	—
South Atlantic	42	23	19	19.2†	11.7†	86.8*
North Carolina	10	3	7	26.9	9.1	173.3
South Carolina	10	3	7	48.2	16.4	284.5
East-Northcentral	9	7	2	3.6†	2.9*	17.8*
East-Southcentral	16	5	11	17.3†	5.9*	132.2†
Tennessee	7	5	2	29.2	19.1	73.7
Mississippi	6	0	6	41.0	—	367.2
West-Northcentral	6	5	1	4.3*	3.7*	26.2
West-Southcentral	12	4	8	8.9*	3.3*	66.0*
Mountain	1	1	0	1.5*	1.5	—
Pacific	14	11	3	7.4*	6.0*	51.7
Washington	7	7	0	21.6	21.6	—
California	5	2	3	4.5†	1.5†	54.7
Unknown	4	4	0	—	—	—
Total	132	86	46	9.2	6.4	58.3

* Not significantly different from expected rate ($P < 0.05$, chi^2 test).
† Significantly different from expected rate ($P < 0.05$, chi^2 test).

Tuberculin status: Because of the interest in the relation of tuberculosis to sarcoidosis, the medical records of sarcoid patients hospitalized during 1957 and 1958 were examined to determine the status of the tuberculin reaction both at the time of entry into the service and at the time of first admission to a hospital. Unfortunately, the results of the tuberculin test upon induction were not recorded in almost one-half of the cases. Results of tuberculin testing at the time of initial hospitalization for sarcoidosis were not recorded in 22 of the cases. The results of the record analysis are tabulated in table 44. It is probably not safe to draw any conclusions from these data in view of the large proportion of persons whose tuberculin status is unknown. The information concerning the tuberculin reaction at the time of initial hospitalization is more complete, and sug-

TABLE 44

TUBERCULIN STATUS OF SARCOID PATIENTS AT TIME OF INDUCTION AND FIRST HOSPITALIZATION, UNITED STATES NAVY AND MARINE CORPS, 1957 THROUGH 1958

Rank and Race	Tuberculin Reaction					
	Induction			Hospitalization		
	Positive	Negative	Unknown	Positive	Negative	Unknown
Officers	—	4	18	5	14	3
Enlisted personnel:						
White	3	38	23	8	45	11
Negro	—	23	23	6	32	8
Total	3	65	64	19	91	22

gests that the proportion of positive reactors could fall somewhere between 12 and 35 per cent, depending upon whether the persons with unrecorded tuberculin reactions were positive or negative. It appears that the officers had a somewhat higher proportion of positive reactors. This is quite possibly related to their greater age.

Discussion

Epidemiologic studies of any disease require the inclusion of all the cases that are occurring in the population under investigation and the exclusion of false-positive cases so as to achieve maximal reliability of results. The increasing incidence of reported sarcoidosis in the United States Navy in recent years suggests either that the actual incidence is increasing or that the disease is being more frequently recognized and reported. Gentry and associates (2) reported that 350 cases occurred among American Armed Forces personnel during World War II. A total of 303 cases was reported for naval personnel during a five-year period when the naval strength was considerably less than that of the war years. The completeness of reporting sarcoidosis at the present time is unknown.

Sarcoidosis is predominantly an asymptomatic disease in naval personnel, usually being detected during a routine physical examination. This fact may be of importance in determining attack rates with regard to age and length of service. It is assumed that the disease will be detected most frequently at those times during the service career when routine physical examinations are performed. For officers, such examinations are given on induction, and then annually, on promotion, and at discharge or retirement. Enlisted men are examined on induction, upon re-enlistment, and at discharge or separation. Annual chest roentgenographic examination of enlisted personnel is generally practiced, but is by no means complete. An examination of data for naval strength will reveal that there is a marked drop in enlisted personnel strength during the fourth year of service, indicating large numbers of discharges at this time. This period in the service career coincides with the period of maximal sarcoidosis rates among enlisted men. Age and length of service are positively correlated so that the maximal enlisted age—specific attack rate during the twenty- to twenty-four-year age group may also be explained by the increased frequency of physical examinations at this time. It is believed that the greater prevalence rate of sarcoidosis among officers is, in part at least, explained by more frequent physical examinations. The maximal rate for officers occurred during the eighth to fourteenth year of service, at which time many officer resignations and promotions occur.

The unusually high incidence of sarcoidosis among members of the Negro race is well known. The tenfold difference in rates between whites and Negroes observed in this study is not entirely explained by the geographic origin of the two groups. The proportion of Negro personnel residing in states of high prevalence is only two to three times the proportion of whites residing in these areas. This does not establish a genetic predisposition to the disease, since different exposures to environmental factors within a given geographic area are known to occur between the two races. Because of lack of information, it was not possible to examine the effects of exposure to rural or urban conditions.

The distribution of sarcoid patients by place of residence is in general agreement with results of similar studies reported by Michael, Gentry, Cummings, and their co-workers, using birthplaces of military veterans (1–3). The South Atlantic and East-Southcentral divisions had significantly higher rates than expected when both races were considered. There were some differences between the races in that Pennsylvania had an unusually high rate and California an unexpectedly low rate among white residents. The rates for Negroes appeared to be high among residents of North Carolina, South Carolina, Florida, Alabama, Mississippi, and Louisiana. The numbers of Negro personnel residing in these states were too small to permit statistical testing of these observations. The apparently high attack rates among whites residing in the state of Washington seemed unique, particularly when only one of the 7 patients was born in that state. Cummings and associates (3) have reported an unusually high incidence among persons born in one of the northern counties of the state. It would seem that there are environmental conditions in Washington which might be conducive to the development of sarcoidosis. It would have been desirable in a study of this type to have studied a larger number of cases so that geographic areas of unusual prevalence could be more accurately defined.

Summary

A total of 303 patients with sarcoidosis was observed among United States Navy and Marine Corps personnel during the years 1954 through 1958. The disease occurred ten times more frequently among Negroes than among whites. There was a statistically significant higher attack rate among officer personnel than among white enlisted men. Maximal attack rates occurred among enlisted men twenty to twenty-five years of age, and during the second to eighth year of service. Maximal attack rates among officers occurred about five years later in age or length of service. It is believed that these specific rates are influenced, but not entirely explained, by the frequency and thoroughness of routine physical examinations. The unusually high prevalence of sarcoidosis among residents of the South Atlantic and East-Southcentral states is in agreement with that previously reported by others. There appeared to be an accumulation of cases among white residents of the state of Washington. Because of the incompleteness of the medical records, analysis of the status of the tuberculin reaction in patients with sarcoidosis was unrewarding.

Acknowledgment

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MORTALITY FROM SARCOIDOSIS IN THE UNITED STATES[1]

IWAO M. MORIYAMA

The mortality records on sarcoidosis in the United States, as in most countries, are relatively short. The 1948 revision of the *International Classification of Diseases and Causes of Death* (1) identified, for the first time, "sarcoid of Boeck" as a discrete category. Prior to this revision, sarcoidosis was classified in the residual category of nonmalignant tumor of other and unspecified organs. In 1949, when the 1948 revision was used for the first time in the United States, only 73 deaths were attributed to Boeck's sarcoid. Since 1949 the number of deaths from sarcoidosis has increased each year. The highest total, 196, was reported in 1956 and 1957. In the period 1949 through 1958, the death rate for sarcoidosis increased from 0.5 per one million population in 1949 to 1.0 in 1958 (figure 48).

The change in mortality has been fairly consistent for both white and nonwhite populations. Although the death rate for sarcoidosis among whites has been considerably lower than that for nonwhites, the rate for whites has almost doubled in the ten-year period, 1949 through 1958. For nonwhites, the increase in mortality has been about threefold. How much of this change in mortality is real and how much is due to increased recognition of the disease cannot be determined. However, the latter factor cannot be ignored in the interpretation of these data.

It is not possible to state at this time how many of the deaths attributed to sarcoidosis were in fact due to the disease. It would be of interest to study the quality of the diagnostic evidence on which medical certification is based for all sarcoid deaths, as has been done for other causes of death (2). While such an inquiry would serve to eliminate a number of deaths for which the diagnostic evidence was weak, it would not be feasible to uncover deaths which should have been attributed to sarcoidosis.

Because of the relatively small number of deaths involved each year, further analysis of the data will be based on averages over a time period.

[1] From the National Office of Vital Statistics, U. S. Public Health Service, Department of Health, Education, and Welfare, Washington, D. C.

Death rate by color and sex: For the period 1954 through 1958, the average death rate for nonwhite males was about six times greater than for white males. For females, the corresponding ratio was about seven. Examination of data for the preceding five-year period, 1949 through 1953, shows substantially the same magnitude of color differential in mortality. These differences, while large, are only about one-half the difference in the estimated frequency of sarcoidosis by color diagnosed in the Veterans Administration hospitals between 1949 and 1956, as reported by Cummings, Dunner, and Williams (3).

There was no significant sex difference between the death rates for the white population. However, for the nonwhites the death rate for females was a little more than 20 per cent higher than that for males.

Death rates by age, race, and sex: The age distribution of death rates for sarcoidosis differs greatly by race. As may be seen in figure 49, the death rate for whites increases slowly by age and reaches a peak in the older age categories. There is no mortality to speak of up to the twenty-five- through thirty-four-year age group. For nonwhites, mortality begins to be a factor ten years earlier, in the fifteen- through twenty-four-year age group. This is not inconsistent with the observations of Cummings, Dunner, and Williams (3), who found that the disease occurred more frequently in Negro veterans younger than thirty years than among whites of the same age group.

For the nonwhites, the death rate increases rapidly with age and reaches a peak at age forty for males and at age thirty for females. There is then a relatively rapid decline in mortality. The death rates by age for nonwhite males show a bimodal distribution. At the extreme ages for all race-sex groups, however, the frequency of deaths involved is relatively low.

There is a certain resemblance between the configurations of the mortality curves for sarcoidosis by age and color and the corresponding curves for respiratory tuberculosis prior to the use of streptomycin and isoniazid for tuberculosis therapy (figure 50). Although the tuberculosis mortality rates for white males in 1950 were

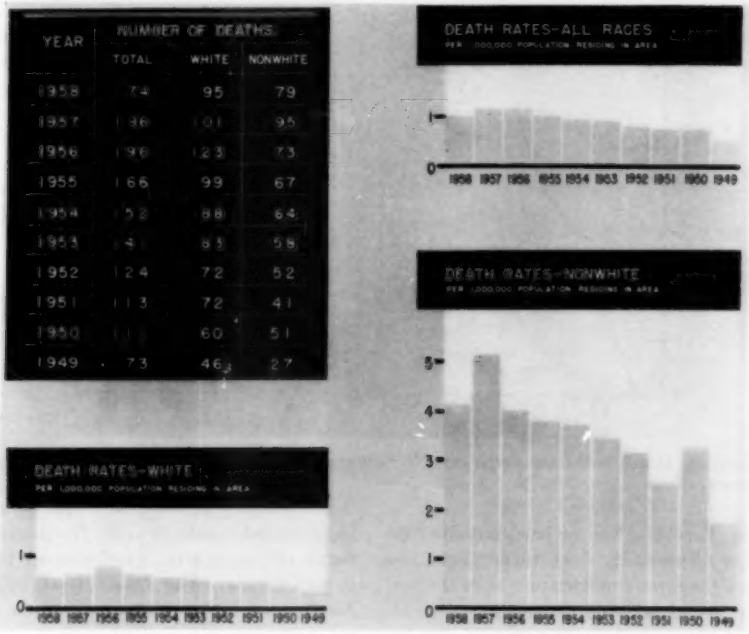

FIG. 48. Trend of sarcoidosis mortality in the United States by color, 1949 through 1958.

much higher than those for white females in the older ages, there is a certain amount of similarity in the general shapes as well as in the manner in which the death-rate curve for white males crosses over that for white females.

Because of the high death rate from sarcoidosis among nonwhite females as compared to that for nonwhite males, there is less of a resemblance between the shapes of the mortality curves for the two diseases in the nonwhite population. However, as is also true for tuberculosis mortality, the sarcoidosis death rate reaches a peak earlier for nonwhite females as compared to that for nonwhite males.

It may be that these points of resemblance in the mortality curves for sarcoidosis and tuberculosis are fortuitous, but mention is made of them because of frequent apparent diagnostic confusion between sarcoidosis and tuberculosis. It may be suggested that mortality data for sarcoidosis are influenced to a marked extent by cases of tuberculosis which are misdiagnosed as

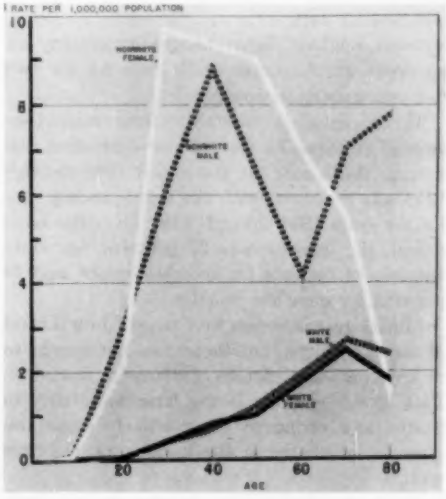

FIG. 49. Death rates for sarcoidosis in the United States by age, color, and sex, 1954 through 1958.

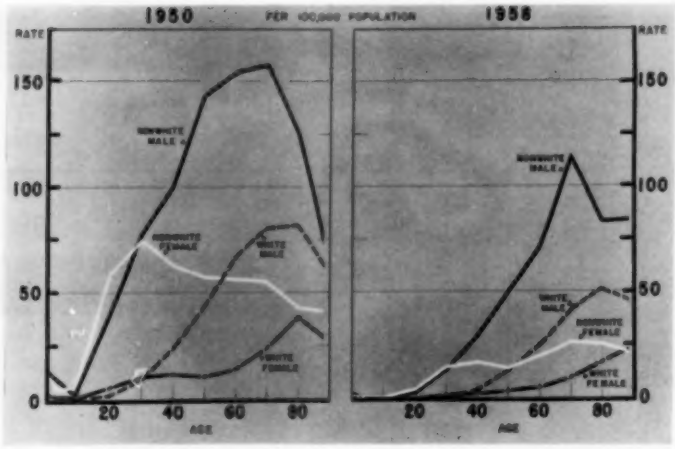

FIG. 50. Death rates for respiratory tuberculosis in the United States by age, color, and sex.

sarcoidosis. This may well be true, but the 1958 distribution of mortality from tuberculosis does not present the same configuration as in the pre-streptomycin and isoniazid period.

Change in mortality by age, color, and sex: Because of the relatively small number of deaths involved, stable measures of change in mortality from sarcoidosis by age, color, and sex cannot be obtained for each subgroup. Generally speaking, however, relatively large changes in mortality are apparent when average death rates for the two five-year periods are compared.

The increase in mortality from sarcoidosis among white males was 45 per cent when the average death rate for the period 1949 through 1953 was compared with the corresponding rate for the years 1954 through 1958. Over the same period, the increase was 37 per cent for white females, 43 per cent for nonwhite males, and 49 per cent for nonwhite females.

Much larger increases were recorded for several of the age groups, but there does not appear to be any consistent pattern of change in mortality. Part of the problem is the large variability in death rates owing to the relatively small frequencies of deaths in the various age-color-sex groups.

Geographic distribution: Average annual death rates were computed for individual states based on data for the nine-year period 1949 through 1957. Even with this consolidation of data, there were sixteen states which recorded, on the average, less than one death per year. The sampling variation is obviously great when data are fragmented in this manner. The lowest death rate was for Nevada, where no deaths from sarcoidosis were reported, and the highest was 2.7 per million population for residents of the District of Columbia. Although not many deaths would be expected for Nevada residents because of the small population, part of the range in the observed death rates can probably be attributed to differences in the recognition of the disease.

The highest death rates appear to be for residents of the South Atlantic states. Other regions which include a number of states with relatively high death rates are the East-Southcentral and the New England states. However, there does not appear to be great consistency in death rates even within a single region where sarcoidosis mortality is relatively high. On the other hand, the death rates for sarcoidosis for the states in the West-Northcentral, the West-Southcentral, and Pacific divisions are consistently lower than the average for the country as a whole. These data by state of residence of the deceased do not appear to lend strong support for the pine pollen hypothesis in the etiology of sarcoidosis, as suggested by Michael and co-workers (4) and Cummings and associates (3).

SUMMARY

Sarcoidosis is a relatively infrequent cause of death in the United States. The recorded deaths

have numbered less than 200 each year since 1949, when annual mortality statistics for this disease entity first became available.

The recorded death rate for sarcoidosis has doubled in the ten-year period 1949 through 1958. The increase has been greater for the nonwhite population than for whites. How much of the increase in mortality is real is not known.

The mortality pattern by age is quite different when color and sex are also considered. There is no difference in rate by sex for the whites, but for the nonwhites the death rate for females exceeds that for males by more than 20 per cent.

There appears to be a certain resemblance in the pattern by age, color, and sex between the present death rates for sarcoidosis and the rates for respiratory tuberculosis prior to extensive use of chemotherapy in tuberculosis. Further study of these patterns may yield useful clues to the nature of sarcoidosis.

Analysis of the geographic distribution of sarcoidosis mortality was not particularly productive because of the small number of sarcoid deaths reported by the states in which the decedents resided.

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SARCOIDOSIS IN NEW YORK CITY[1]

HANS ABELES, ARTHUR B. ROBINS, AND AARON D. CHAVES

As part of our tuberculosis survey program, we collected data on prevalence rates for sarcoidosis in New York City since 1956. In 1956 we surveyed a district with a predominantly Negro population. Among 81,000 roentgenograms studied, we found prevalence rates of 70 per 100,000 population for sarcoidosis, and 170 for tuberculosis. The sarcoidosis rate in the age group of twenty to twenty-nine years was 180 for females and 60 for males. The tuberculosis rate in a similar but not identical age group was 150 for females and 160 for males. In other words, the prevalence rate for sarcoidosis was higher than that for tuberculosis in females of this age group.

In the same year a health center was opened in a predominantly white, middle-income area, and 12,000 people were examined roentgenographically in this district. We did not find a single case of sarcoidosis, but the prevalence rate for active tuberculosis was 70 per 100,000 population. In the following year another health center was opened in a predominantly white area. We surveyed 90,000 people, and the prevalence rate was 7 for sarcoidosis and 80 for tuberculosis per 100,000 population.

Last year we carried out a survey in the East Harlem area, which has a population consisting of approximately 55 per cent Puerto Ricans, 35 per cent other whites, and 10 per cent Negroes. Among 52,000 persons examined roentgenographically, we obtained rates of 32 for sarcoidosis and 96 for tuberculosis per 100,000 population. In females, the prevalence rates for sarcoidosis and tuberculosis were identical, 43 per 100,000 population.

We are now in the process of surveying the Harlem area with its predominantly Negro population. So far, approximately 50,000 persons have had roentgenograms, and only the survey diagnosis is available. The rate for active tuberculosis in the Harlem area is about 135 per 100,000 population. It is expected that this figure will eventually be somewhat smaller because it includes all cases of active tuberculosis, and some of these cases had been found and recorded previously. The sarcoidosis rate in the Harlem area is about 50 per 100,000 population. I would like to emphasize that these are preliminary rates since the survey has not been completed.

In summary, the young females have a sarcoidosis prevalence rate approximately equal to the tuberculosis rate in areas of New York City with predominantly Negro and Puerto Rican populations. For a variety of reasons we have not been able, so far, to break down our data as to such factors as place of birth and length of residence in New York City.

[1] From the Bureau of Tuberculosis, the City of New York Department of Health, New York, New York.

Discussion

DR. CUMMINGS: The floor is now open for questions or comments on the last three papers and on Dr. Abeles' interesting but brief report.

DR. SMITH: You will recall the very large numbers of sarcoid cases from North Carolina and South Carolina; we were also shown the actual cases in Virginia plotted on the geographical chart (*see* figure 47). I was raised in South Carolina, have lived most of my life in North Carolina, and have traveled all over the state. Almost every one of the sarcoid cases shown us was from the "sand" land of North Carolina, South Carolina, and Virginia—not the red clay or yellow clay land. So this pinpoints the site of occurrence of the disease much more sharply than if you considered the whole state.

The peanut business is in the Virginia "sand" land. The northern half of North Carolina produces peanuts. The southern half of the North Carolina coast does not grow peanuts, and neither does South Carolina. So I do not know where that leaves peanuts so far as the etiology of sarcoidosis is concerned.

DR. MICHAEL: To comment further on the map Dr. Smith referred to, it follows quite closely, as indicated, the earlier studies of the World War II military personnel and the more recent studies of the veteran population. You will recall that in one of the studies it was pointed out that these patients were concentrated below the Fall Line, which is precisely the area that Dr. Smith is commenting on. This is the sandy soil area, particularly in the South. Being from Georgia, may I speak on that state for a moment?

You will remember that there was a tremendous cluster of cases in the southern part of Georgia, the most sparsely populated region in the state; and for those of you who have not taken the drive

from northern Georgia down through the state, the concentration of cases begins just about at the place where the red clay stops and the sandy soil and scrub pine begin.

DR. DUBLIN: Having vacated the chair, I feel it is permissible for me to discuss these papers. My first question has to do with Colonel Cooch's presentation.

It is a technical point, but I think it is rather important. Colonel Cooch related the cases that were discovered in discharge examinations, if I remember his presentation correctly, to the total force of the military at that time.

Would it not provide a more precise measurement to compare the number of cases discovered with the total number of discharges? The bulk of the Army is not "exposed" to the same screening device as those who are going through a discharge process. I think the case ratios derived in this manner would have been considerably higher than those reported by Colonel Cooch, and perhaps more meaningful, since they would then relate to the universe from which the cases were selected.

My second point is that, as an epidemiologist, I am impressed with the importance of pursuing each major lead until one is satisfied that the inferences drawn from his observation are supported by the facts. It seems to me that the initial studies undertaken by the Veterans Administration right after the war did not really answer any questions; rather, they pinpointed some intriguing questions, namely, the meaning of the peculiar geographic distribution of sarcoid in the population under study.

I have asked Dr. Cummings (and I was referred by him to Dr. Max Michael who, in turn, referred me to others) why, having turned up these index cases, somebody did not expend a little shoe leather by going back to the communities from which these people came, and undertaking comparative epidemiologic studies within those families or communities in which the cases were discovered. I know that some efforts were made, but I have never seen accurate or complete data reported on such observations. It seems to me that we are now getting more and more cases reported by the Army, the Navy, and various other sources. The inference is that the disease itself is not directly related to military service, but has its origins prior to induction, and may be related to the environment in which these people were born. Is it not appropriate then to get at the basis of some of these interesting questions of whether the determining factors are pine pollen, peanuts, or other factors not yet identified, by wearing out some shoe leather to get the data?

DR. CUMMINGS: Dr. Cooch, would you respond to the first question raised by Dr. Dublin?

DR. COOCH: Well, to answer Dr. Dublin's question about taking the discharge population: He is quite right; it would have been better. The only trouble is that in a retrospective study you have to take the population you can get, and there are no breakdowns for discharge populations in this respect.

DR. CUMMINGS: The second question, I think, can go to anyone bold enough to respond. Why has there not been more "shoe leather epidemiology"?

DR. MICHAEL: There was shoe leather epidemiology, but it is unpublished. May I take one moment to describe it?

Of the original group of over 300 patients, the random sample consisted of 13 patients, all of whom were interviewed in their homes, using the technique of "shoe leather epidemiology." The first person who was seen had worked in a turpentine still. All of the remainder seen thereafter worked in the lumber or turpentine industries. They all lived in areas where these were the major industries.

The next facet was to repeat this, which was done in the Virginia area. Immediately the turpentine and lumber dropped out. A smaller study was done, through Rochester, New York, and scattered all along the line.

DR. CUMMINGS: We are getting into some history here, and I think the Chairman would be remiss if he did not get into the record an acknowledgment to Dr. John Ransmeier who, while working in the National Academy of Sciences, made the first observation of a remarkably skewed distribution of sarcoidosis occurring among military personnel.

I would like at this time to call on Dr. Ransmeier and ask him whether he would comment on the papers he has heard today.

DR. RANSMEIER: This observation was something that any one of you would have made; we had the data before us, collected with the help of Dr. Beebe and his staff and through the cooperation of the Armed Forces. It was easy because all the tissues from these cases were submitted to the Armed Forces Institute of Pathology, which made it very simple to get a roster. Dr. Beebe and his staff put these data on cards, and it was very simple to see where these people were born and where they came from. But what interests me is that this distribution of higher prevalence in the Southeast holds up today, twelve years later. Whatever factor was operating then apparently is still operating, despite the fact that during those years we have had tremendous shifts of population. I still remain intrigued by this, and hope that some day somebody will explain it.

SUMMARY

PHILIP E. SARTWELL

The three reports just presented permit us to make certain statements about the distribution of sarcoidosis in the United States with greater confidence than has been possible hitherto. It seems to me that the reports from the Army and Navy are quite consistent in their major features.

The reason for special attention to epidemiologic studies of sarcoidosis in the armed services, of course, is that such studies can more readily be conducted within a closed population, in which medical services are relatively uniform and complete and routine roentgenography of the chest is practiced. Furthermore, military records are kept in uniform fashion, and the knowledge of characteristics of the population at risk is somewhat better than in the general population.

It may be helpful to enumerate some points of agreement, and a few of disagreement, between the Army and Navy incidence studies and the mortality study. The latter, I believe, provides the first systematic and inclusive observations on the occurrence of sarcoidosis in this country but, of course, mortality data in a disease of this character are of limited usefulness. Several points need to be kept in mind when attempting to interpret the mortality rates. Sarcoidosis is an infrequent disease. It is difficult to diagnose reliably, requires a certain degree of medical sophistication to recognize, and is recognized more frequently in situations in which chest roentgenograms are commonly employed. It is easily confused with a number of other conditions. It leads directly to death rather infrequently, cor pulmonale being a common immediate cause of death. In the United States, with its marked mobility of population, the state of residence at time of death may not be even in the same part of the country where the individual lived prior to onset of the disease; this is especially true of the nonwhite cases.

Both the Navy and the mortality studies indicate that over the last decade the recognized frequency of sarcoidosis has at least doubled. However, increasing recognition, as opposed to increasing occurrence, must, for the present, be assumed to be the more probable explanation.

All three studies are in agreement in finding sarcoidosis to be several times more common in the nonwhite population: an estimated ten to sixteen times in the Armed Forces studies, and six times in the mortality study. Since the certification of sarcoidosis as a cause of death may be less complete for nonwhite persons, it is not surprising that some disparity exists. Adding this to the previous evidence, the much greater incidence in Negroes can be considered as thoroughly established, at least for the United States.

Sex distribution, from the mortality study, seems to be uniform among whites, but mortality in nonwhites appears to be a little greater in females.

The age distribution of recognized cases in the services is probably dependent in part on methods of case finding, and it seems doubtful whether any firm statements can be made. The mortality data give us a rather remarkable picture, on which I should like to dwell for a moment. For whites, the mortality rate increases rather steadily up to age seventy in both sexes. For nonwhites, after an abrupt rise from childhood to age twenty, there is a tendency for mortality rates to be uniform or, in females, even to decline slightly beyond the age of thirty. A host-susceptibility factor may be involved in these differences.

The geographic distribution revealed by the Army and Navy data with respect to residence at entry into the service is roughly in keeping with that indicated by previous Army and Veterans Administration studies. The mortality rates present a somewhat different picture. Thus, the rank order of regions with respect to death rates from sarcoidosis among both whites and nonwhites, taken separately, finds the New England states highest, the Middle Atlantic states near the top, and the South Atlantic states around the middle. There is a slight downward gradient in mortality as one proceeds from north to south on the East Coast. Were it possible to obtain rates by state of birth, this picture might well be altered for the nonwhite cases. Differences in medical practice in different sections may also, as previously mentioned, introduce spurious differences in rates. The Armed Forces and Veterans Administration data are largely free from this form of bias.

The armed services studies point toward a higher frequency in persons who have lived in rural places, as have several previous studies. The mortality data were not examined with respect to this issue.

The following two points seem deserving of special emphasis:

(*1*) The regional correlation between white and nonwhite rates is not very good from either the Navy or the mortality study; that is, the regions with high frequency among whites do not regularly have high frequency among nonwhites.

(*2*) The variation in mortality between regions

is much greater for nonwhites than whites, allowance being made for the difference in size of the respective populations.

The several notable differences seen between whites and nonwhites, and between geographic areas, might perhaps be explained on the basis of some combination of host susceptibility and exposure factors, but such explanations would be labored and unconvincing at this time. They might also be explained by the hypothesis that what we call sarcoidosis consists of two or more diseases, each present in different proportions in the white and nonwhite population.

The one inescapable conclusion that can be drawn from these very interesting data is that more study of the problem is needed. Can we suggest any lines of investigation that might be especially profitable? It is my belief that certain types of study have not been sufficiently pursued. I refer to careful retrospective investigations of individual cases with detailed inquiry as to past residence, occupations, diet, and living conditions. To be of any value, there will have to be carefully chosen matched control subjects and probably several kinds of controls, matched for different attributes of the cases.

One such study will be reported by Dr. Comstock at a later session. Another, by Dr. Buck, is now going on in Baltimore, and is yielding information of considerable interest with regard to the sensitivity of patients, their first-degree relatives, and their controls to two antigens, tuberculin and *Candida albicans* extract. He is also securing illuminating data as to the familial aggregation of the disease. Studies of this kind cannot be pursued in the hospital or clinic alone. They necessitate repeated visits, often at inconvenient times, to the homes of subjects, and a high degree of patience and persuasiveness. They also demand a combination of clinical, laboratory, and epidemiologic skills.

GEOGRAPHIC EPIDEMIOLOGY OF SARCOIDOSIS

MARTIN M. CUMMINGS, *Moderator*

INTRODUCTION

DR. CUMMINGS: Geographic distributions of diseases in the past have suggested clues to etiology. We are all familiar with the so-called "goiter belt" relating to thyroid disease and more recent studies of multiple sclerosis, which offer a new direction for study of this baffling entity. This section of the program was planned to provide information on the geographic distribution of sarcoidosis on a global basis. Although we anticipate obtaining incomplete and preliminary data, it still seems important to learn whether sarcoidosis differs in distribution from tuberculosis (a finding which might indicate that these diseases are not different clinical manifestations produced by the same organism), or whether sarcoidosis has a distribution similar to other diseases or syndromes (which might suggest some common genetic or environmental influence). For these reasons, among others, it is hoped that the papers which follow may send us home with new ideas for future studies.

GEOGRAPHIC EPIDEMIOLOGY OF SARCOIDOSIS IN FLORIDA[1]

C. F. McCUISTON, MAX MICHAEL, JR., AND PAUL C. HUDGINS

Epidemiologic studies of recent and remote vintage have indicated certain intriguing geographic patterns of sarcoidosis. These appear noteworthy and offer promising clues to the elusive etiology of this protean disease.

In much of the earlier literature, the rural nature of the disease was alluded to (1–3). Studies of sarcoidosis occurring in members of the United States Armed Forces during World War II confirmed this rural distribution and pointed out the heavy concentration of cases in the southeastern United States (4). The striking predominance of disease in the Negro was also noted. Survey of a large number of cases in veterans corroborated these findings and extended the geographic pattern somewhat (5). Other observations in this country have been in agreement with the above studies in most instances (6, 7).

Possible clues to be read into the epidemiologic studies to date are the following: (*1*) If sarcoidosis is a form of tuberculosis, it does not follow the epidemiologic pattern usually associated with that disease. (*2*) It would seem that either etiologic agents are concentrated in the areas of high incidence or else persons residing in these areas are highly susceptible to the possible offending agents. Perhaps elements of both may prove to be correct.

The thought that sarcoidosis might represent the naturally occurring form of beryllium disease was engendered by correlation of certain epidemiologic findings with available geologic data (8). Corroborative evidence to support this hypothesis, however, has not been forthcoming.

The suggestions that sarcoidosis might be related to exposure to pine pollen also arose from study of epidemiologic data (9). A correlation between the birthplaces of United States veterans with sarcoidosis and the distribution of pine trees has been noted. Whether such association is purely fortuitous remains to be seen. To gather further data concerning this, the following studies were carried out in a somewhat restricted locale.

Since the concentration of pine trees varies significantly in the different regions of the state of Florida, this area was chosen for study.

The distribution of pine trees in the state of Florida in billions of board feet is shown in figure 51. It will be noted that the heaviest concentration of pine trees is in the northeastern section, and the lowest in the southern part of the state. Thus, it may be seen that were intimate associa-

[1] From the Veterans Administration Sarcoidosis Research Laboratory and the Jacksonville Hospitals Educational Program, Inc., Jacksonville, Florida.

FIG. 51. Concentration of pine trees in various sections of Florida: NW—northwest; NE—northeast.

tion with pine trees to be related in some fashion to sarcoidosis, a varying incidence of the disease would be anticipated in the different areas of the state. A group that serves admirably to test this hypothesis was furnished by the Florida State Board of Health, whose cooperation in this venture is gratefully acknowledged.

Approximately 500,000 seventy-millimeter survey films are taken by the Board of Health each year. Any abnormalities noted are checked on 14- by 17-inch films. We have reviewed reports of 200,000 of these large films taken in a ten-year period, beginning in January, 1950. All reports indicating either bilateral hilar adenopathy or suspected sarcoidosis were used for the study. There were 296 subjects with probable adenopathy and 109 with suspected sarcoidosis. Questionnaires as to place of birth and residence history were sent to all patients, and replies were received from more than two-thirds. Further information was obtained from physicians and hospital records, when available. Of the 296 patients with probable hilar adenopathy, 247 were retained in this study. In 56 of this group, sarcoidosis was definitely proved. Since current evidence indicates that bilateral hilar adenopathy in the age groups under study usually represents the earliest manifestations of sarcoidosis (10, 11), these cases are also included. In the second group, 56 definitely proved cases of sarcoidosis, exclusive of the bilateral hilar lymphadenopathy syndrome, were included.

The yearly incidence of hilar adenopathy and tuberculosis per 100,000 roentgenograms are indicated in table 45. Thus, it may be seen that during the period under study there has been a definite decrease in the finding of tuberculosis. When the incidence of hilar adenopathy and sarcoidosis is combined, a definite increase in incidence over the ten-year period is noted. This latter, of course, may represent more proficiency in reading films rather than an actual increase in the instance of the disease. Obviously, however, it has not decreased as has tuberculosis. This trend is similar to that reported in Sweden by Wallgren (12).

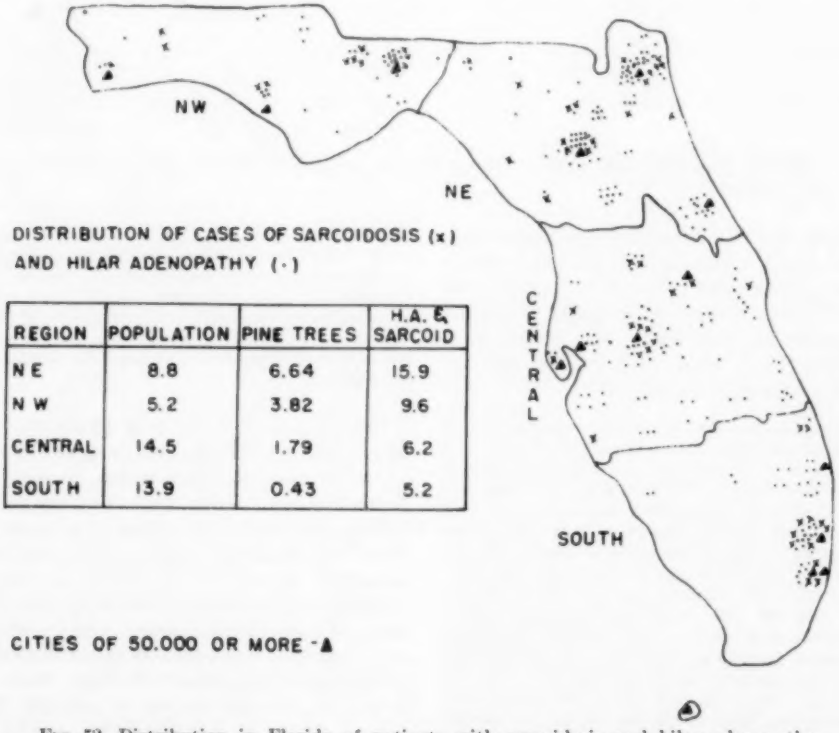
When the place of longest residence of these patients is presented, several interesting features are noted (figure 52). Although there appears to be an even distribution of the cases throughout the state, a closer perusal of distribution as to population and pine tree density shows the converse. Thus, in the northeastern section, with a population of 880,000, and 6.6 million board feet of pine trees, the incidence is 15.9 cases per 100,000 roentgenograms. The incidence of cases decreases sectionally with the decreasing concentration of pine trees. For example, the southern section, with 1.4 million population, has only 5.2 cases per 100,000 roentgenograms, and this corresponds with the decrease in pine tree density. Although the cases seem to concentrate in the population centers, in actuality they are grouped in the rural areas adjacent to the population centers.

It is shown in table 46 that, numerically, 70 per cent of the state's population is classified as urban and 30 per cent as rural; yet the amount of sarcoidosis was at least equal, if not greater, in the rural areas. Extensive skin testing with several delayed-type skin-testing antigens, in-

TABLE 45

YEARLY INCIDENCE OF HILAR ADENOPATHY AND TUBERCULOSIS PER 100,000 ROENTGENOGRAMS

Year	Tuberculosis Case Rate	Hilar Adenopathy Case Rate	Sarcoidosis Case Rate	Sarcoidosis plus Hilar Adenopathy Case Rate
1950	416.0	2.4	—	2.4
1951	500.0	3.1	0.8	3.8
1952	478.0	4.1	0.8	4.8
1953	429.0	1.8	1.0	2.8
1954	310.0	3.8	1.3	5.1
1955	261.0	4.3	0.5	4.9
1956	220.0	3.9	1.7	5.6
1957	204.0	5.3	1.7	7.0
1958	281.0	8.6	1.5	10.1
1959	Not reported to date			



REGION	POPULATION	PINE TREES	H.A. & SARCOID
NE	8.8	6.64	15.9
NW	5.2	3.82	9.6
CENTRAL	14.5	1.79	6.2
SOUTH	13.9	0.43	5.2

FIG. 52. Distribution in Florida of patients with sarcoidosis and hilar adenopathy, according to place of longest residence. NW—northwest; NE—northeast; H.A.—hilar adenopathy.

TABLE 46

RURAL-URBAN DISTRIBUTION OF SARCOIDOSIS, BILATERAL HILAR LYMPHADENOPATHY, AND TUBERCULOSIS

Group	Urban	Rural
	per cent	*per cent*
Total population	70	30
Bilateral hilar lymphadenopathy	56	44
Sarcoidosis	41	59
Tuberculosis	90	10

cluding P-1 (purified protein pine pollen antigen), PPD, and PPD-B (prepared from nonphotochromogenic unclassified mycobacteria) were performed in three counties (figure 53). Columbia County is in a heavily forested area, where lumber and turpentine are the major industries. About 50 per cent of the population there were positive to the P-1 antigen; 22 per cent were positive to the P-1 in Highlands County, a predominantly agricultural area; and only 5 per cent were positive to P-1 in Key West, where there are no pine trees at all. All but one of those with positive reactions had lived in areas forested with pine trees at some time. The decreasing incidence of positive reactions to pine pollen antigen in these three counties is clearly shown.

A comparison of reactions to pine pollen, PPD, and PPD-B in these different areas is shown in figures 54 and 55. It was noted that, in patients with sarcoidosis, the reaction to pine pollen was of the lowest order. The incidence of reactions to pine pollen in the other groups was similar to that for controls. Of interest was the increased sensitivity to pine antigen and PPD-B in patients with inactive sarcoidosis. That this does not represent negative evidence of a relationship of sarcoidosis and pine pollen hypersensitivity, one need only recall the general paucity of positive cutaneous reactions to a variety of antigens in these patients.

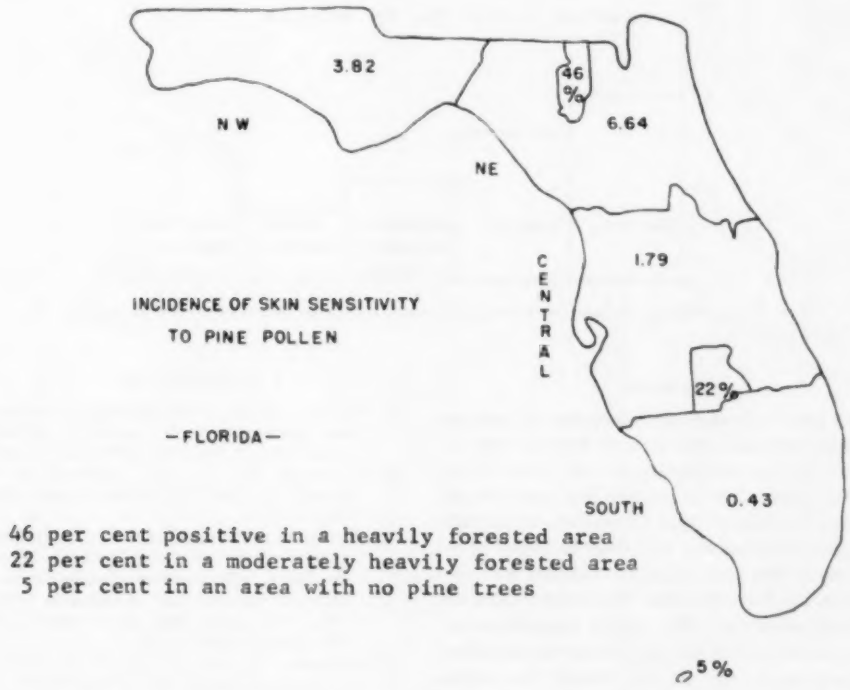


FIG. 53. Incidence of skin reactivity to purified pine pollen protein in normal subjects in various sections of Florida.

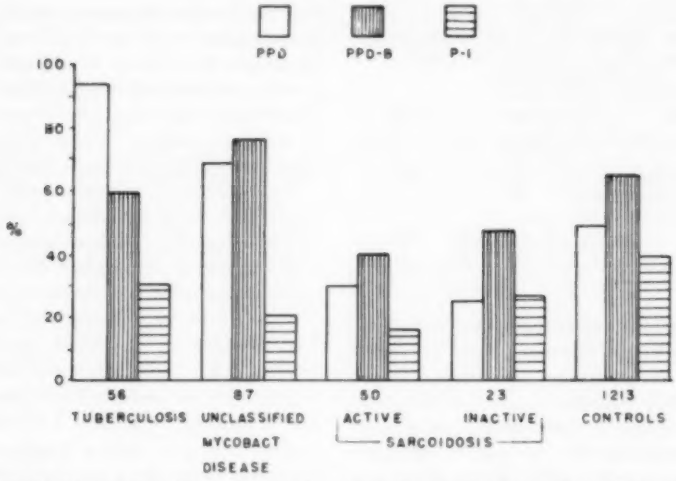


FIG. 54. Incidence of positive skin reactions to various antigens in tuberculosis, unclassified mycobacterial disease, and sarcoidosis (in per cent).

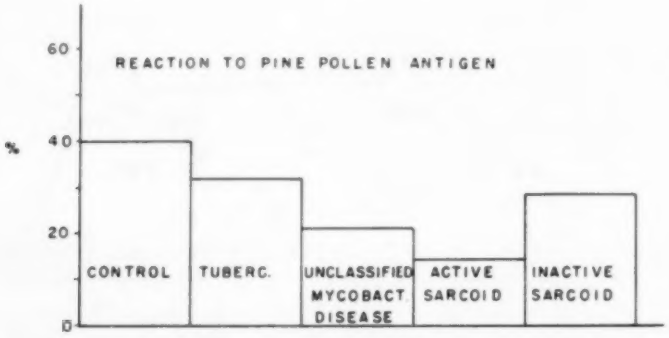


FIG. 55. Incidence of positive pine pollen skin reactions in various disease groups (in per cent).

SUMMARY

We have indicated the association of patients with sarcoidosis in the state of Florida with the regions of highest density of pine trees. Skin-testing studies have indicated that pine antigen produces a delayed type of reaction in patients residing in such areas. The lower incidence of reactions to this pine antigen in patients with sarcoidosis has been discussed. It is believed that the findings presented offer further suggestive evidence of the role of the pine tree in the causation of sarcoidosis, but do not furnish noncontrovertible evidence.

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CLAY EATING AND SARCOIDOSIS[1]

A Controlled Study in the State of Georgia

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Introduction

The Muscogee County Tuberculosis Study, located in Columbus, Georgia, was established in 1946 for the purpose of combining effective tuberculosis control and a broad basic epidemiologic study of tuberculosis (1). Among the major activities of the study was an extensive and continuous program of case finding, with principal emphasis on chest photofluorography. Unlike the practice in some tuberculosis clinics, all persons whose photofluorograms suggested potentially serious chest abnormalities were recalled for further investigation, regardless of whether the abnormalities were thought to be tuberculous or nontuberculous. In this way, many persons with various chest diseases have been identified in the community, including a number who were thought to have sarcoidosis. Because of the possibility that sarcoidosis might be related in some way to tuberculosis, an attempt was made to obtain long-term observations on all persons with the sarcoid syndrome. No systematic study of these persons was made until 1957, eleven years after the initiation of the Muscogee County Tuberculosis Study.

At that time, two of the writers visited a nearby kaolin "mine." In the course of conversations there, three statements were made which suggested that sarcoidosis might be associated with clay eating. First, the workers at the mine were frequently asked by outsiders, usually Negro females, to bring them a supply of the white clay, which was considered highly desirable for eating. Apparently clay eating was not a thing of the past, as we had naively believed, but was still practiced to a considerable extent (2–4). Indeed, we were informed that such clay was commercially available (5). Second, we were told that the American kaolin-type of clay contained a small amount of beryllium,[2] which is known to produce sarcoid-like lesions as a result of certain types of exposure (7). Finally, this type of clay was said to be most common along the fall-line in the southeastern part of the United States, paralleling to some extent the geographic distribution of sarcoidosis in this country (8). These bits of information suggested that sarcoidosis might in some way be related to eating clay. When 6 of the next 7 patients with sarcoidosis who were seen in the clinic admitted to having eaten clay, we decided to undertake a study of the relationship of clay eating and sarcoidosis.

Procedures

Because of the low prevalence of sarcoidosis, it appeared that a retrospective or case-control type of study would be most suitable. The cases were drawn in 1957 from the files of the Muscogee County Tuberculosis Study by selecting all persons whose records showed a diagnosis of sarcoidosis, suspected sarcoidosis, or hilar adenopathy of unknown origin, and who, in addition, were not known to have died or to be residing outside the metropolitan area of Columbus, Georgia. Furthermore, only those cases identified more than one year prior to the study were selected. This last condition was imposed to allow sufficient time for both diagnostic procedures and continued observation to rule out conditions which might at first be confused with sarcoidosis, such as malignant neoplasms, tuberculosis, or atypical pneumonia.

Although the 141 persons so identified are not a complete or representative sample of potential cases of sarcoidosis in the community, they are not a highly selected group since they had been garnered from 350,000 chest roentgenograms made between 1946 and 1956 in a community of about 160,000 persons. Of these examinations, 130,000 had been obtained in community-wide surveys in 1946 and 1950. The rest were obtained in small surveys and examinations made by the Health Department clinics for many different purposes. There is reason to believe that most cases of sarcoidosis in the community diagnosed outside the clinics have also been examined by the study.

Two matched controls were selected for each case. Because the cases had been recognized as the result of a chest roentgenogram, the controls were also drawn from the population which had roentgenograms for the same reason within a month of the date on which the patient was examined. The controls also matched the patients for race and sex and for stated age within five years. In addition, they were matched for resi-

[1] From the U. S. Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C.

[2] However, recent analyses of kaolin from this "mine" show no evidence of beryllium (6).

dence within similar socioeconomic subdivisions of the area at the time of examination and, whenever a choice was still possible, for marital status and occupation. When a matched control was found to have moved away or to have died, another control was drawn in the same fashion.

Two sets of information were desired from both cases and controls. The first was a history of clay eating or related pica; the second was an examination which would allow a more definitive decision as to the presence or absence of sarcoidosis. It seemed essential that both history and examination be performed similarly for cases and controls, that the history be obtained without knowledge of whether the subject was a case or a control, and that the examination be done without knowledge of the history of clay eating. There was some fear that the subjects might consider clay eating to be a socially unacceptable practice and might be reluctant to admit this habit. To avoid undue emphasis on clay eating, other questions were added to the routine history. Three of these questions were thought to have a possible relationship to sarcoidosis. These were contact with tuberculosis, rural residence, and the use of spring water. Fifteen other questions were included to make it appear that we were studying health habits in general. Five of these questions were related to the condition of the subject's present health. Another 5 concerned the use of tobacco in various forms. The remaining five requested information about occupation, the number of children, cravings in pregnancy, and the use of candy and chewing gum. The final attribute studied, a history of previously positive serologic tests for syphilis, was available for most of the study population from Health Department records.

A field investigator was employed to locate the subjects and to obtain answers to the questionnaire. She did not know which subjects were cases and which were controls, and she was deliberately kept ignorant of the primary purpose of the study. When each schedule was completed, it was mailed directly to Washington so that the clinic workers could have no knowledge of the responses to the interview.

All subjects were also urged to come to the clinic for examination. This included a brief medical history and physical examination, with special reference to organ systems likely to be involved in sarcoidosis, roentgenograms of the chest in the posteroanterior and lateral projections, roentgenograms of both hands, a tuberculin test with 5 TU (0.0001 mg.) of PPD-S, and a determination of serum albumin and globulin. Kveim tests were not done because of conflicting reports of their usefulness and because of the long period of observation necessary for interpretation (9, 10).

In order to obtain a classification of the chest roentgenographic findings which would not be influenced by the other clinical findings, the initial and final chest roentgenograms were read by one of the authors (DJS) who did not know the results of the final clinic examinations or the answers to the questionnaires. The blood specimens were examined by Dr. Wray Tomlinson of The Medical Center, Columbus, Georgia, and were identified only by number. Albumin and globulin determinations were made by the biuret method after "salting out" the serum with 22.5 per cent ammonium sulfate (11).

Of the 141 cases originally selected, 50 had to be excluded at the outset: 40 patients were found to have moved away, 4 could not be located, 4 had died, one had been diagnosed as not having sarcoidosis, and one refused to participate. The remaining 91 cases were evaluated by the clinic physician on the basis of all available evidence. Twelve patients who were considered to have been essentially negative at all times and 5 who could be classified only as having hilar adenopathy were excluded from the analysis. The remaining 74 persons comprise the cases in the present study. All of them were considered to have sarcoidosis on the basis of roentgenographic findings, skin sensitivity, serum globulin, and clinical course. In only 2 instances was it possible to obtain biopsies, both of which showed findings consistent with sarcoidosis. The low proportion of cases confirmed by pathologic examination illustrates the practical difficulties in persuading persons without serious symptoms to submit to surgery. On the other hand, insistence on pathologic confirmation of the diagnosis of sarcoidosis may well produce a group of cases so highly selected that they are no longer representative of cases of sarcoidosis as a whole.

Results

Comparison of cases with their matched controls showed that the two groups were identical with respect to race-sex composition and, as may be seen in table 47, almost the same with respect to average age. When asked for an appraisal of their current health, both groups responded similarly. Histories of recent medical examinations were also similar except that more of the patients had roentgenograms within the past year. This discrepancy presumably reflects the attempt of the clinic to keep sarcoid cases under observation as long as a visible abnormality persisted. Among male subjects, the number of children was the same for cases and controls. Among females, however, the average number of children was greater for cases than controls, a finding which suggests that there may be an association of pregnancy and sarcoidosis.

The race-sex-age characteristics of the study cases are shown in table 48. There were more Negroes than whites, and more females than males. Most of the patients were between the ages of twenty-five and forty-five at the time of

TABLE 47

COMPARISON OF CASES AND CONTROLS, SARCOID STUDY, MUSCOGEE COUNTY, GEORGIA

	Cases	Controls
Number in study group	74	148
Mean age in years	36.8	36.7
Self appraisal of health		
Excellent	15%	13%
Good	58%	57%
Fair	23%	26%
Poor	4%	4%
Medical examination in past year		
Visit to physician	77%	78%
Physical examination	64%	66%
Chest roentgenogram	64%	54%
Mean number of children		
Female subjects	3.1	2.4
Male subjects	2.6	2.6

TABLE 48

DISTRIBUTION OF CASES BY RACE, SEX, AND AGE, SARCOID STUDY, MUSCOGEE COUNTY, GEORGIA

Age at Selection	Race and Sex				
	Total	White Males	White Females	Negro Males	Negro Females
Total	74	6	23	15	30
15–24	4		1		3
25–34	33	3	12	9	9
35–44	27	2	10	4	11
45–54	3			1	2
55+	7	1		1	5

the study. Although it was not feasible to obtain prevalence ratios of sarcoidosis in the community, the distribution of cases in relation to total persons examined was consistent with the impression that sarcoidosis is most frequent in young adult life, more common among Negroes than whites, and more common among females than males.

The classification of chest roentgenographic findings in the study cases is shown in table 49. The comparison is limited to initial and final films, and does not reflect the fairly frequent occurrence of transient changes in the extent and nature of the chest lesions. Two patients with extrathoracic lesions had normal chest films. Slightly more than half of the patients showed only hilar adenopathy on the initial film. At the time of the study, one to eleven years after the initial diagnosis, half of the total group of cases had normal chest roentgenograms. Only one-sixth had evidence of increased thoracic disease. Thus, it seems likely that a large proportion of the cases had "burned-out" sarcoidosis at the time of the present study. It may be mentioned in passing that no bone lesions were detected in the films of the hands. One cystic lesion in the clavicle appeared while the patient was under observation.

The mean serum protein concentrations for cases and controls are shown in table 50. Serum albumin was almost the same, on the average, for patients and controls. Serum globulin levels, on the other hand, were significantly higher among patients, both for the groups as a whole and on the basis of comparisons with their matched controls. The globulin levels were highest for patients with new or increased disease demonstrable on the final film and lowest for

TABLE 49

INITIAL AND FINAL ROENTGENOGRAPHIC CLASSIFICATION OF CASES, SARCOID STUDY, MUSCOGEE COUNTY, GEORGIA

Initial Classification	Final Classification				
	Total	Normal	Decrease or No Change	Increase or New Component	No Final Film
Total	74	38	21	11	4
Normal	2	2			
Hilar only	43	21	12	8	2
Pulmonary only	11	4	3	3	1
Pulmonary and hilar	18	11	6		1

TABLE 50

MEAN SERUM ALBUMIN AND GLOBULIN LEVELS AMONG PATIENTS AND CONTROLS, BY RACE AND SEX, SARCOID STUDY, MUSCOGEE COUNTY, GEORGIA

Race-Sex Group	Number Examined		Serum Albumin Gm./100 Ml.		Serum Globulin Gm./100 Ml.	
	Cases	Controls	Cases	Controls	Cases	Controls
Total	60	122	4.78	4.86	2.95	2.47
White males	6	10	4.90	5.30	2.45	2.00
White females	18	37	5.03	4.91	2.40	2.21
Negro males	12	27	4.53	4.85	3.18	2.51
Negro females	24	48	4.64	4.73	3.38	2.76

patients whose final films were read as normal. As noted in a previous paper, Negroes had higher serum globulin levels than whites (12).

At the time of the initial diagnosis, 85 per cent of the cases showed less than 5 mm. of induration to 5 TU of PPD-S. At the time of the present study, 74 per cent of the cases and 61 per cent of the controls were nonreactors to this dose of tuberculin. Although PPD prepared from the Battey strain of unclassified mycobacteria was not used in 1957, an effort has been made in recent months to test cases and controls with this antigen. Of the 37 cases tested to date, only 32 per cent reacted to 5 TU of PPD-B, compared with 49 per cent of the controls. It is, therefore, not likely that these cases represent disease caused by unclassified mycobacteria. Nor is it likely that many of the cases were really histoplasmosis, since only 2 of 28 cases were reactors to histoplasmin.

Of the 20 attributes elicited by questioning both patients and controls, only 6 appear to have any likelihood of being associated with sarcoidosis. These are shown in table 51. Three attributes (those marked with an asterisk in the table) were thought to have a possible association with sarcoidosis prior to the study. A history of clay eating in adult life was found twice as often among patients as among controls, a difference which might have occurred by chance only once in 20 trials. More sarcoid patients had a history of rural residence at some time than controls, but this difference could have occurred by chance once in 8 trials. The difference is slightly less if the number of years of rural residence is taken into account. Fewer patients with sarcoidosis gave histories of tuberculosis among their blood relatives than did the controls, but this difference could have occurred by chance once in 5 trials. If household association with a case of tuberculosis, as determined from the records of the Muscogee County Tuberculosis Study, is used as the attribute, essentially the same difference is found. Although the negative association of family tuberculosis with sarcoidosis is not statistically significant, it is unlikely that chance might have obscured a strongly positive association.

Among the other 16 attributes investigated, only 3 appeared to be associated with sarcoidosis. A history of cigarette smoking without other tobacco use was less than half as frequent among patients as among controls. This difference seems quite unlikely to have arisen as the result of chance alone. The use of chewing tobacco and the frequent eating of candy were both more common among patients than among controls. The likelihood that the associations could have occurred by chance alone were once in 5 and once in 14 trials, respectively.

TABLE 51

ATTRIBUTES ASSOCIATED WITH SARCOIDOSIS, SARCOID STUDY, MUSCOGEE COUNTY, GEORGIA

Attribute	Per Cent With Attribute		Relative Risk†	Confidence Level
	Cases	Controls		
Clay eating in adult life*	21	10	2.3	.95
Use of chewing tobacco	16	8	2.2	.81
Frequent candy eating	22	12	2.1	.93
Rural residence at some time*	59	49	1.5	.87
Cigarette smoking, no other tobacco use	23	40	0.4	.98
Family history of tuberculosis*	8	16	0.5	.81

* Assumed to be associated with sarcoidosis prior to study.

† Relative risk was calculated by the method proposed by Cornfield (13), in which relative risk equals p_1q_2/p_2q_1 in which p_1 is the prevalence of the attribute among cases, p_2 the prevalence of the attribute among controls, q_1 the prevalence of the absence of the attribute among cases, and q_2 the prevalence of the absence of the attribute among controls.

The presence of at least one of four attributes, clay eating in adult life, frequent candy eating, chewing tobacco, or no use of cigarettes, increased the relative risk of sarcoidosis nearly fourfold as compared with the risk to persons without any of these attributes. However, the presence of combinations of these four attributes in a given individual did not appear to yield a further increase in the relative risk, but the numbers of such cases were much too small for any firm conclusions.

DISCUSSION

In searching for a possible meaning of these observations, the possibility arises that clay eating and chewing tobacco on the positive side, and cigarette smoking and a family history of tuberculosis on the negative side, might all be associated primarily with rural residence. How-

ever, when persons with and without a history of rural residence were examined separately, essentially the same relationship with these four attributes was observed. Similarly, adjustment for rural residence did not alter the observation that female patients had had more children than female controls. Rural residence does not seem to be the common thread binding these attributes together.

A number of considerations suggest that none of the attributes investigated in this study is likely to play an etiologic role in sarcoidosis. A history of clay eating during adult life was obtained only from Negro females and, although we are certain that the true prevalence of clay eating is higher than the responses to the interview indicate, it seems unlikely that a majority of the patients were clay-eaters. Denial of cigarette smoking and a history of frequent candy eating were associated almost entirely with sarcoidosis among whites, while the use of chewing tobacco was associated with sarcoidosis only among white males and Negro females. None of these four attributes was associated with sarcoidosis among Negro males. The most likely explanation of these findings is that the observed attributes are associated with still another attribute, which in turn is etiologically related to sarcoidosis.

Although the significance of these rather queer findings is far from clear, some useful information does emerge from this study, primarily because it is possible to compare patients with sarcoidosis with a group of matched controls. First, it appears that pregnancy might be a predisposing factor for sarcoidosis. Second, there is no indication that sarcoidosis is related to tuberculosis. Finally, patients with sarcoidosis have been shown to differ in a number of attributes from a comparable group of normal persons. Even though the interpretation of these differences does not seem possible at this time, the use of the case-control method of investigation offers a good hope of providing clues to many of the mysteries of sarcoidosis, provided the investigator is smart enough—or perhaps lucky enough—to ask the right questions.

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GEOGRAPHIC EPIDEMIOLOGY OF SARCOIDOSIS IN DENMARK: 1954–1957[1, 2]

OLE HORWITZ

Introduction

The present study is an account of the incidence of pulmonary sarcoidosis in different regions of Denmark in the years 1954 through 1957. Further, the geographic pattern of sarcoidosis is examined in its relationship to the extent of coniferous forest and the occurrence of tuberculosis.

[1] From the Danish Tuberculosis Index; and the Finseninstitutet og Radiumstationen, Dermatological Department, Copenhagen, Denmark.

[2] This work was supported in part by grant E-3812 from the Institute of Allergy and Infectious Diseases, National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland.

Material and Methods

Pulmonary sarcoidosis: The incidence of pulmonary sarcoidosis, hereafter referred to as sarcoidosis, is evaluated from the number of cases diagnosed in chest clinics during the years 1954–1957, inclusive. A central chest clinic had been established in each county in Denmark by the year 1945 (1).

All cases were diagnosed by experienced chest specialists. The diagnostic criteria in the various chest clinics can, by and large, be regarded as uniform. Only cases classified as pulmonary sarcoidosis are included in the study. Cases of disease with diagnoses such as "observation for sarcoidosis" and "hilar adenitis," not otherwise specified, are thus not included.

In the majority of counties, the number of new cases of sarcoidosis was obtained from the annual

TABLE 52

Incidence of Pulmonary Sarcoidosis in the Counties of Denmark, 1954–1957

Region	County	Number of Cases				Annual Average	Annual Rate Per Million
		1954	1955	1956	1957		
Capital*		28	26	19	16	22.3	30
Zealand	Copenhagen County	26	17	21	19	20.8	52
	Roskilde	†	†	4	2	3.0	36
	Frederiksborg	2	5	2	4	3.3	20
	Holbæk	7	8	2	2	4.8	38
	Sorø	5	3	10	4	5.5	43
	Præstø	3	3	2	3	2.8	23
	Maribo	3	8	6	5	5.5	41
Bornholm		3	1	2	2	2.0	41
Funen	Svendborg	5	7	8	4	6.0	40
	Odense	3	14	19	14	12.5	49
Jutland	Vejle	16	29	22	25	23.0	111
	Skanderborg	†	22	†	†	22.0	161
	Århus	9	9	10	3	7.8	37
	Randers	10	6	5	5	6.5	38
	Ålborg	15	28	31	17	22.8	98
	Hjørring	†	†	†	†	†	†
	Thisted	2	4	5	3	3.5	40
	Viborg	11	5	1	5	5.5	34
	Ringkøbing	20	18	12	55	26.3	133
	Ribe	15	13	19	20	16.8	94
	Southern Jutland	10	7	8	5	7.5	35
Total						230.2	55

* Excluding the municipality of Frederiksborg, for which data were not available.
† Data not available.

TABLE 53

INCIDENCE OF PULMONARY SARCOIDOSIS IN DIFFERENT REGIONS OF DENMARK, 1954–1957

Region	Population in 1955	Number of Cases	Annual Rate Per Million
Capital*	753,361	89	30
Zealand†	1,155,894	182	39
Bornholm	48,632	8	41
Funen	404,583	74	46
Jutland I‡	954,151	443	116
Jutland II§	840,769	123	37
All Denmark* §	4,157,390	919	55

* Excluding the municipality of Frederiksberg.

† For Roskilde County, data were not available for 1954 and 1955. The number of cases in these years was computed from the number reported in 1956 and 1957.

‡ Comprises the following counties: Ribe, Ringkøbing, Vejle, Skanderborg, and Ålborg. For Skanderborg County, data were not available for 1954, 1956, and 1957. The number of cases in these years was computed from the number reported in 1955.

§ Remainder of Jutland, excluding Hjørring County.

reports of the chest clinics. When such data were not available, it proved possible to collect the figures by personal communication from all but two areas, as shown in table 52. In a few counties, however, the statistics comprised cases diagnosed over a period of only one or two years. The incidence of sarcoidosis gives the number of cases diagnosed annually per million population; the census figures for 1955 were used in the calculations (2). The annual incidence for the period 1954–1957 as calculated for each county is shown in table 52.

Counties with uniform incidence of sarcoidosis were grouped into larger geographic regions, as shown in table 53. To test the validity of the grouping, the observed and expected number of cases for each county was calculated. The results are shown in table 54. The expected number of cases is the number that would be observed if the incidence for the county had been the same as in the corresponding region. A comparison of the observed figures with the expected figures for the counties showed that the grouping was valid since the deviations were not statistically significant.

Coniferous forest: The relative extent of coniferous forests in the individual counties is presented in terms of the percentage of the total area overgrown with conifer (table 55). The calculations are based on the survey made in 1951 (3). In these calculations, no account was taken of mixed growth since the survey did not include information on the proportion of conifers in mixed growth. However, this error can be considered insignificant because the 1951 survey indicates only 0.7 per cent mixed growth. Since the data also showed that conifers constitute two-thirds of all forests and plantations in Denmark, and assuming that this also applies to the mixed growth, then the percentages quoted for coniferous forests in the counties should be increased by an average of 0.5 per cent, i.e., by about one-tenth.

Geographic tuberculin pattern in the general population: There are no data to elucidate the geographic tuberculin pattern for the entire population. However, the mass campaign of 1950–1952 provides a good indication of the pattern among the 15- to 34-year-old persons in the provinces. These data show that 65 per cent of those invited

TABLE 54

THE OBSERVED* AND EXPECTED† NUMBER OF CASES OF PULMONARY SARCOIDOSIS IN THE COUNTIES OF THE DIFFERENT REGIONS

Region	County	Observed Number of Cases	Expected Number of Cases
Zealand	Copenhagen County	83	62
	Roskilde	12	13
	Frederiksborg	13	25
	Holbæk	19	20
	Sorø	22	20
	Præstø	11	19
	Maribo	22	21
	Total	182	180
Funen	Svendborg	24	28
	Odense	50	47
	Total	74	75
Jutland I	Vejle	92	96
	Skanderborg	88	63
	Ålborg	91	108
	Ringkøbing	105	92
	Ribe	67	83
	Total	443	442
Jutland II	Århus	31	31
	Randers	26	25
	Thisted	14	13
	Viborg	22	24
	Southern Jutland	30	31
	Total	123	124

* The number of cases observed during the years 1954–1957.

† The number of cases which would be observed if the incidence for the county were identical with the incidence for the whole region.

TABLE 55

FORESTS AND PLANTATIONS IN DENMARK IN 1951, DIVIDED ACCORDING TO AREA AND TYPE OF TREE (DECIDUOUS/CONIFEROUS), BY COUNTIES

Region	County	Total Area	Area Overgrown with Forests and Plantations				
			Deciduous	Mixed Growth Including Copsewood		Conifers	
			Area	Area	Percentage of Total Area	Area	Percentage of Total Area
		ha*	ha*	ha*		ha*	
Zealand, Lolland-Falster	Copenhagen County	49,345	2,384	132	0.3	539	1.1
	Roskilde	69,053	3,137	112	0.2	1,370	2.0
	Frederiksborg	134,371	11,088	581	0.4	7,942	5.9
	Holbæk	175,206	5,841	615	0.4	3,997	2.3
	Sorø	147,822	10,661	630	0.4	4,569	3.1
	Præstø	169,259	14,461	369	0.2	4,590	2.7
	Maribo	179,770	13,201	570	0.3	3,148	1.8
Bornholm		58,755	1,800	2,322	4.0	5,623	9.6
Funen	Svendborg	166,666	10,865	1,315	0.8	4,014	2.4
	Odense	181,559	6,335	1,656	0.9	3,517	1.9
Jutland	Vejle	234,799	9,541	1,684	0.7	10,687	4.6
	Skanderborg	171,926	6,526	2,945	1.7	17,303	10.1
	Århus	80,439	3,750	727	0.9	2,152	2.7
	Randers	246,583	6,062	1,684	0.7	13,439	5.5
	Ålborg	291,412	4,848	1,750	0.6	13,628	4.7
	Hjørring	286,542	2,685	2,243	0.8	13,546	4.7
	Thisted	177,358	349	2,110	1.2	13,403	7.6
	Viborg	304,982	4,551	1,740	0.6	16,594	5.4
	Ringkøbing	465,972	760	1,520	0.3	36,052	7.7
	Ribe	306,920	1,784	2,010	0.7	22,986	7.5
	Southern Jutland	396,396	8,631	3,435	0.9	12,161	3.1
Total Denmark†		4,295,135	129,260	30,150	0.7	211,260	4.9

* 10,000 hectares (ha) corresponds to about 25,000 acres.
† Capital excluded.

to participate in the campaign did so.[3] The participants may be regarded as representative of the general population with respect to factors of tuberculosis epidemiology within the ages in question (4).

For the various counties, the percentage of participants fifteen to thirty-four years old who were tuberculin negative[4] is shown in table 56. Among the participants, there was a total of nearly 149,000 who were vaccinated with BCG prior to the mass campaign. They have been included in this study as tuberculin nonreactors, irrespective of the results of the tuberculin testing at the mass campaign. This was done for two reasons: (*1*) The great majority of these vaccinations were performed in the years 1948–1952, i.e., shortly before the mass campaign, and (*2*) since the infection rate has been very low in recent years (5), only very few of these persons could be expected to have been infected in the period between the vaccination and the mass campaign. Therefore, no significant error has been committed by including the vaccinated cases as tuberculin negative, and whatever error does exist can be considered of the same order of magnitude in the different counties.

Geographic tuberculin pattern among cattle: There has been extensive tuberculin testing of cattle in Denmark since the 1930's in the campaign

[3] The population invited to the mass campaign comprised that of the provinces, but excluded some minor areas and "removers." This covers the great majority of the 80,000 by which the study population falls short of the census population.

[4] Induration less than 6 mm. after Mantoux, 10 TU. The same criterion was used in two counties where Mantoux, 5 TU, was used.

TABLE 56

TUBERCULIN-NEGATIVE SUBJECTS AMONG PERSONS AGED FIFTEEN TO THIRTY-FOUR YEARS EXAMINED IN THE DANISH MASS CAMPAIGN, 1950–1952*

Region	County	Total Population Aged 15-34 Years (Census 1950)	Tuberculin Reaction Read in the Mass Campaign	Tuberculin Nonreactors†	
				Number	Per Cent
Zealand	Roskilde	22,200	11,012	7,748	70
	Frederiksborg	42,696	15,924	10,635	67
	Holbæk	33,462	19,103	13,101	69
	Sorø	35,095	21,589	15,318	71
	Præstø	33,231	14,481	10,622	73
	Maribo	36,481	25,863	19,531	76
Funen	Svendborg	39,940	23,821	17,382	73
	Odense	70,308	37,046	26,211	71
Jutland	Vejle	57,432	35,642	21,830	61
	Skanderborg	37,056	21,280	13,610	64
	Århus	57,803	27,442	17,067	62
	Randers	46,084	27,148	16,172	60
	Ålborg	65,914	35,848	20,623	58
	Hjørring	48,243	29,211	17,815	61
	Thisted	23,770	16,507	9,955	60
	Viborg	42,748	26,566	15,671	59
	Ringkøbing	55,642	29,428	16,583	56
	Ribe	49,537	25,148	14,923	59
	Southern Jutland	56,419	36,593	17,738	49
Total		854,061	479,652	302,535	63

* 14,356 persons whose vaccination status before the mass campaign could not be established are excluded.

† 148,617 persons BCG-vaccinated prior to the mass campaign are included as tuberculin nonreactors, irrespective of the result of the tuberculin testing.

against bovine tuberculosis. Thus, 48 per cent of all herds were tuberculin-tested in 1937 and 97 per cent in 1943. The tuberculin pattern among cattle is evaluated from the 1937 tests, and reported by the State Veterinary Department. For the individual counties, the percentage of tested herds which were without tuberculin reactors is shown in table 57.

Geographic pattern of pulmonary tuberculosis: The incidence of pulmonary tuberculosis was obtained from the official statistics contained in the Medical Report for the Kingdom of Denmark (6). This gives the number of new cases of pulmonary tuberculosis reported from the individual counties. Pulmonary tuberculosis is reportable by law. Notifications, i.e., reports, made on separate forms, go into a nationwide central register, established in 1921. The Danish notification system and tuberculosis program may be regarded as so reliable that a real expression of the incidence of the disease is obtained (7, 8). In the present study the incidence rates for 1955 were calculated from the number of cases reported during a three-year period, 1954 through 1956, in order to avoid chance fluctuations (table 58).

RESULTS

Incidence of sarcoidosis, 1954–1957: During the years 1954–1957, approximately 900 cases of sarcoidosis were diagnosed in Denmark. This corresponds to a mean annual rate of 55 per million population. As may be seen in table 53, the incidence rate was not uniform in the various regions of Denmark. In the capital, on Zealand, Funen, Bornholm, and in the region designated as Jutland II, the rate was approximately uni-

TABLE 57

HERDS WITHOUT TUBERCULIN REACTORS IN THE COUNTIES OF DENMARK, 1937

Region	County	Number of Herds	Number of Herds Tested	Herds without Reactors	
				Number	Percentage of Herds Tested
	Copenhagen County	4,458	1,963	1,303	66
	Frederiksborg	5,194	2,986	2,141	72
Zealand	Holbæk	10,005	5,633	3,403	60
	Sorø	7,208	4,477	3,015	67
	Præstø	8,785	4,681	3,761	80
	Maribo	7,843	3,207	3,008	94
Funen	Svendborg	10,471	4,362	3,868	89
	Odense	10,657	1,376	1,166	85
	Vejle	10,867	6,897	3,272	47
	Skanderborg + Århus	12,628	7,641	2,975	39
	Randers	10,861	5,212	1,806	35
	Ålborg	11,323	4,531	2,175	48
Jutland	Hjørring	13,806	5,886	3,419	58
	Thisted	9,070	8,180	4,277	52
	Viborg	14,616	7,669	2,742	36
	Ringkøbing	15,646	3,822	1,467	38
	Ribe	11,733	5,774	2,130	37
	Southern Jutland	13,774	5,746	1,253	22
Total Denmark		188,945	90,043	47,181	52

form, around 40 per million. The differences in incidence between these regions were not significant at the 5 per cent level. In Jutland I, however, a region comprising five counties with a population just under 1 million, the rate was much higher, 116 per million.

The incidence of sarcoidosis in Jutland I, therefore, was three times that for the remainder of Denmark. The probability that this difference is due to chance is less than 1 per cent. The higher rate is thought to result from the more frequent occurrence of sarcoidosis. However, it cannot be overlooked that this difference may be influenced by administrative factors. Presumably, such factors were responsible for the number of cases in Ringkøbing County which rose to 55 in 1957 from approximately 17 in previous years. It should be added, however, that, even if the year 1955 is excluded from the analysis, the rate in this county is more than 100 per cent higher than in the remainder of Denmark, namely, 84 per million.

Sarcoidosis incidence, coniferous forest, and tuberculosis: In the subsequent discussion, the possibility of a correlation is sought between the incidence of sarcoidosis and the presence of coniferous forests or tuberculosis. An attempt has been made to illustrate this by diagrams in which the incidence of sarcoidosis in a county is plotted as ordinate, while the presence of coniferous forests or tuberculosis are plotted as abscissa. A positive correlation would be revealed if the incidence of sarcoidosis increased as the variable on the abscissa increased.

The relation between sarcoidosis and coniferous forests for the individual counties is indicated in figure 56. There is apparently a group of counties for which a positive correlation exists. However, this impression disappears when the two counties with the highest sarcoidosis incidence are excluded, Ringkøbing and Skanderborg. As previously pointed out, the incidence in Ringkøbing County is probably too high as a result of administrative factors. In Skanderborg County the incidence is based on the number of cases diagnosed in a single year, as shown in table 52. It must, therefore, be concluded from this study that there does not appear to be an association between the occurrence of sarcoidosis and coniferous forests, as has been observed by others (9).

The relationship between sarcoidosis and tuberculosis is demonstrated in figures 57, 58, and 59. That there is no correlation between the incidence of sarcoidosis and the geographic tuberculin pattern in the general population is shown in figure 57. However, this comparison cannot be considered quite correct. The tuberculin pattern used referred to those who were fifteen to thirty-four in 1950–1952, and should properly have been correlated with the incidence of sarcoidosis among those in the same cohort, i.e., those who were twenty to thirty-nine years old in 1956. This could not be done because the age distribution of the sarcoidosis cases was not given in the official reports. As shown in figure 58, there is no correlation between the incidence of sarcoidosis and the geographic tuberculin pattern for cattle in 1937; there is no correlation between the incidence of sarcoidosis and pulmonary tuberculosis in 1955, as shown in figure 59.

TABLE 58

THE INCIDENCE OF PULMONARY TUBERCULOSIS IN DENMARK IN 1955

Region	County	Number of Cases Reported 1954–1955–1956	Annual Rate per 100,000
Capital		1,409	54
Zealand	Copenhagen County	353	30
	Roskilde	55	22
	Frederiksborg	108	22
	Holbæk	64	17
	Sorø	67	17
	Præstø	57	16
	Maribo	45	11
Bornholm		11	8
Funen	Svendborg	132	29
	Odense	233	31
Jutland	Vejle	130	27
	Skanderborg	89	22
	Århus	155	25
	Randers	111	22
	Ålborg	221	32
	Hjørring	131	25
	Thisted	30	12
	Viborg	106	22
	Ringkøbing	129	22
	Ribe	118	22
	Southern Jutland	156	24
All Denmark		3,910	29

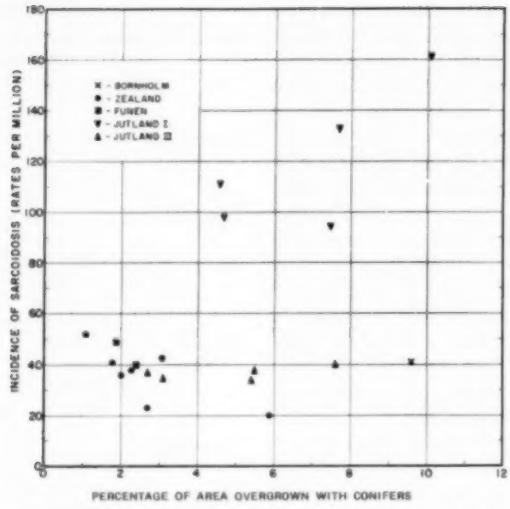
INCIDENCE OF SARCOIDOSIS (RATES PER MILLION)
PERCENTAGE OF AREA OVERGROWN WITH CONIFERS
× - BORNHOLM
● - ZEALAND
■ - FUNEN
▼ - JUTLAND I
▲ - JUTLAND II

FIG. 56. The correlation between the incidence of sarcoidosis and the prevalence of conifers, by county and region.

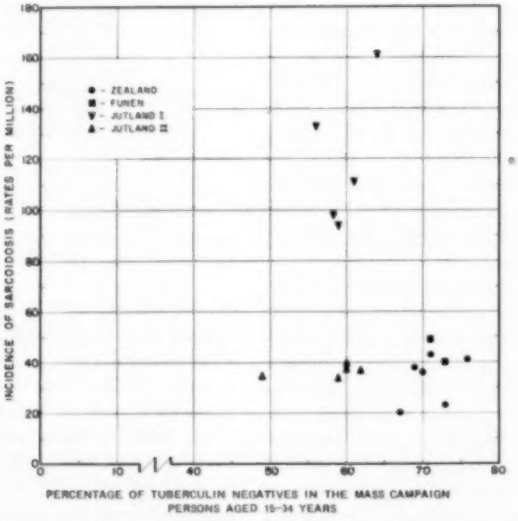
INCIDENCE OF SARCOIDOSIS (RATES PER MILLION)
PERCENTAGE OF TUBERCULIN NEGATIVES IN THE MASS CAMPAIGN
PERSONS AGED 15-34 YEARS
● - ZEALAND
■ - FUNEN
▼ - JUTLAND I
▲ - JUTLAND II

FIG. 57. The correlation between the incidence of sarcoidosis and the prevalence of tuberculin nonreactors in the Danish mass campaign, 1950–1952, by county and region.

DISCUSSION

It is recognized that the present study of sarcoidosis has not satisfied the ideal requirements. For instance, the study was not based on individual notifications to a central, nationwide register. Thus, double registration of the patients owing to migration from one county to another may have occurred, but this can be regarded as a minor error. It must also be pointed out that the representativeness of the data is not shown

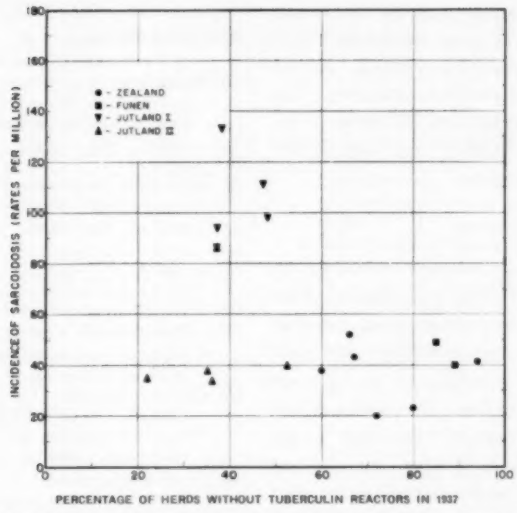
INCIDENCE OF SARCOIDOSIS (RATES PER MILLION)
PERCENTAGE OF HERDS WITHOUT TUBERCULIN REACTORS IN 1937
● - ZEALAND
■ - FUNEN
▼ - JUTLAND I
▲ - JUTLAND II

FIG. 58. The correlation between the incidence of sarcoidosis and the prevalence of tuberculin-negative herds, by county and region.

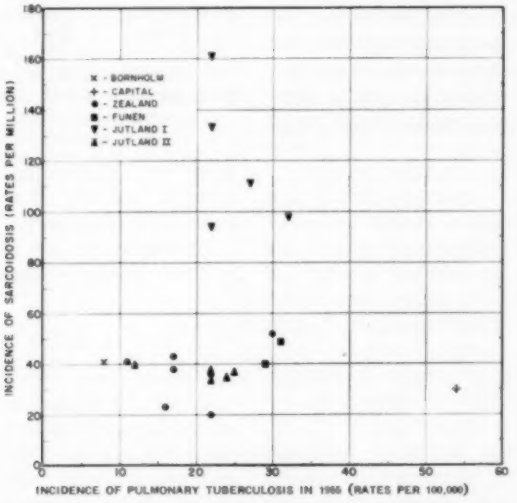
INCIDENCE OF SARCOIDOSIS (RATES PER MILLION)
INCIDENCE OF PULMONARY TUBERCULOSIS IN 1955 (RATES PER 100,000)
× - BORNHOLM
+ - CAPITAL
● - ZEALAND
■ - FUNEN
▼ - JUTLAND I
▲ - JUTLAND II

FIG. 59. The correlation between the incidence of sarcoidosis and the incidence of tuberculosis, by county and region.

numerically, i.e., there is no indication of the extent to which the data represent all sarcoidosis cases diagnosed in Denmark during the period of investigation. Undoubtedly, the majority of new cases is represented since close cooperation exists between chest clinics and other hospitals, as well as with general practitioners. The registration deficit presumably is of the same magnitude in the various counties, so that it is hardly reasonable to explain the various incidences on this basis.

In spite of the various shortcomings, the re-

sults of the present study may be considered valid, by and large. It must be stressed that these shortcomings could be rectified, as was done with Danish tuberculosis statistics. The conditions would then be created for more intensive studies on the epidemiologic and clinical characteristics of sarcoidosis.

Summary

The incidence of pulmonary sarcoidosis in Denmark during 1954–1957 was obtained from the number of cases reported by chest clinics in individual counties. Approximately 900 cases were reported, corresponding to an average annual rate of 55 per million. The incidence was uniform in different regions of Denmark except for a greater part of Jutland where the rate was three times as high as in the rest of the country.

There was no correlation between the geographic pattern of sarcoidosis and coniferous forests, and none was found with the tuberculin pattern in the general population as shown by the participants in the mass campaign of 1950–1952 who were fifteen to thirty-four years of age; the geographic tuberculin pattern in cattle in 1937; the geographic pattern for the incidence of pulmonary tuberculosis in 1955.

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SARCOIDOSIS IN SCOTLAND[1]

ANDREW C. DOUGLAS

Epidemiology

No special study has been made so far of the incidence of sarcoidosis in the various parts of Scotland, and the only figures available on which an estimate of the incidence can be based are those provided by mass miniature roentgenographic surveys. The year 1958 was a particularly active one for mass roentgenography in Scotland, and the rate per 1,000 cases of thoracic sarcoidosis discovered that year by units operating from 5 main centers is shown in figure 60: Aberdeen, Dundee, Glasgow, Lanark, and Edinburgh.

It is of some interest to relate these figures to the pine-bearing areas of Scotland. The pine forests lie almost entirely to the east of a line between the Firth of Forth and Inverness, and it is interesting to note that the highest incidence of sarcoidosis was recorded from Aberdeen, which is adjacent to the greatest concentration of pine woods anywhere in the British Isles. It will be noted, however, that a relatively low incidence was reported from the Dundee region, which is within the forested area, and a relatively high incidence from Lanark, which is outside the area of forestation.

No firm conclusions can be drawn from information of this type, but the fact that there are apparently quite wide variations in incidence in different regions of the country suggests that more detailed epidemiologic studies of this kind might be rewarding.

Review of 100 Cases

In the past eight years, approximately 150 cases of sarcoidosis have been seen in the chest clinics of Edinburgh, Scotland. This paper is concerned with the results of an analysis of the first 100 of these cases for which adequate data were available, the principal purpose of the review being to discover the fate of two groups of patients of particular interest to the chest physician.

A preponderance of female patients has often been noted in previous studies of sarcoidosis, and in the present series 79 per cent of the patients were female.

[1] From the Northern General Hospital, Edinburgh 5, Scotland.

The cases have been classified into three groups according to presenting manifestations (figure 61):

(*1*) Forty-eight patients presenting with enlargement of hilar lymph nodes, with or without associated paratracheal involvement.

(*2*) Thirty-two patients presenting with pulmonary opacities.

(*3*) A group of 20 patients presenting with miscellaneous lesions. Among the miscellaneous lesions were included important and persistent enlargement of liver and spleen; lesions in bone and subcutaneous tissues; involvement of kidney, pancreas, pituitary and salivary glands; cranial nerves; nasal mucosa; and patients with iridocyclitis and skin lesions, excluding erythema nodosum.

The youngest patient in the series was a girl of 14 with pulmonary opacities, and the oldest was a woman of 76, presenting with iridocyclitis.

In the first two groups, the greatest incidence fell in the third and fourth decades. In the group with miscellaneous lesions, however, the greatest incidence was in the fifth decade and, as far as could be determined, 85 per cent of the patients in this group first developed lesions after the age of 40.

Of the 48 patients with hilar nodes or hilar and paratracheal nodes, the disease in 4 is too recent for further consideration. Thirty-nine of the 44 patients remaining (89 per cent) showed spontaneous and complete regression of the enlarged nodes within 2 years (figure 62). On an average, regression began at 4 months, with a range of 1.5 to 7 months, with complete regression at an average of 8.3 months, with a range of 4 to 20 months.

In 5 cases, transient pulmonary opacities developed when the nodes began to regress, clearing spontaneously by the time they were completely resolved. Of the 5 remaining cases, constituting the 11 per cent which did not spontaneously resolve at 2 years, there are 3 patients with nodes persisting at 2, 2½, and 7 years; and 2 who developed persisting pulmonary opacities. No patient undergoing spontaneous regression has shown further sarcoid manifestations in subsequent follow-up study ranging from 6 months to 5½ years.

For the purpose of analysis, patients with pul-

FIG. 60. Incidence of sarcoidosis in Scotland.

monary opacities from all groups have been considered together, a total of 44 cases, and 33 of these have been observed to roentgenographic stability. Spontaneous and complete clearing of pulmonary opacities occurred in 19 (58 per cent) of the 33 cases. More than half had cleared by one year, and all but one had cleared by 2 years. The exception showed slow but complete clearing over 41 months (figure 63). In no case of spontaneous clearing of pulmonary opacities have further sarcoid manifestations been noted in follow-up study ranging from 6 months to 6 years.

Thirteen of the 33 patients with pulmonary opacities have been treated with corticosteroids. Treatment was given for pulmonary opacities which were progressing after 6 months of observation or were unchanged after one year.

The contrast between the patients whose disease relapsed on the withdrawal of steroids or on reducing the dosage below a critical level and those whose disease did not relapse after withdrawal of steroids is shown in figure 64. The disease in 7 patients had relapsed on withdrawing steroids.

In 2 cases (*N.McB.* and *N.S.*), withdrawal of

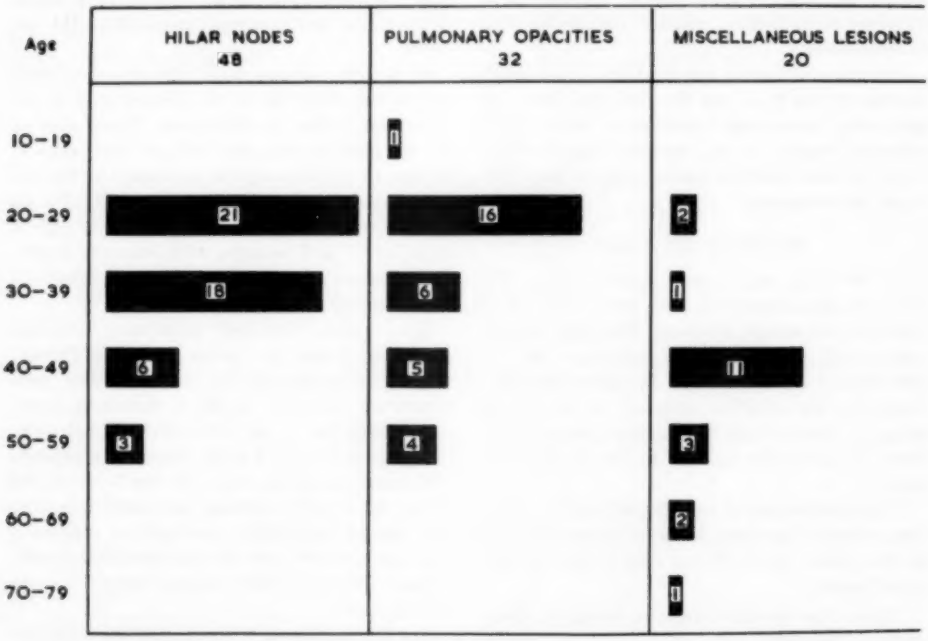

FIG. 61. Age distribution of 79 female and 21 male patients with sarcoidosis.

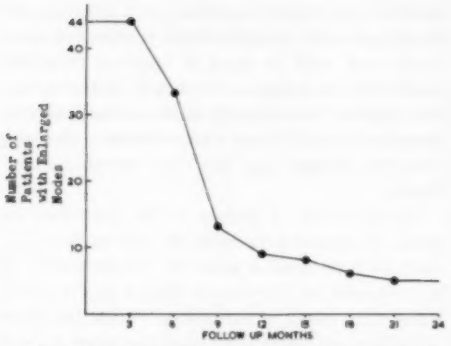

FIG. 62. Spontaneous resolution of hilar nodes in 44 cases.

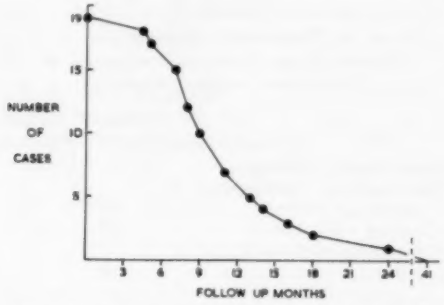

FIG. 63. Spontaneous clearing of pulmonary opacities in 19 cases.

steroids after 2 and 6 months resulted in roentgenographic relapse, but these patients got well without further treatment at 13 and 24 months, respectively. In these cases, the giving of steroids was regarded simply as an incident in patients undergoing spontaneous recovery, and they have, therefore, been included in the group showing spontaneous recovery.

The disease of patient *E.N.* relapsed on withdrawal of treatment at 5 months and was re-treated. Treatment continues at 35 months because some slight opacities remain, but it now seems likely that these opacities represent residual fibrosis.

The disease of patient *T.C.* recurred on reduction of prednisolone dosage below 7.5 mg. per day at 6 months and is being re-treated.

Patient *D. F.* has had 3 episodes of relapse at 6, 12, and 40 months on attempting to withdraw steroids. It is now evident that this patient will also have slight residual pulmonary fibrosis when, if ever, the activity of the sarcoid process finally wanes. This patient had sarcoid manifestations for more than 10 years before treatment, and he illustrates the point that the longer sarcoid manifestations have existed, i.e., the more chronic the disease, the longer treatment may be expected to continue.

Patient *H.W.*'s disease relapsed at 7 months when she stopped treatment of her own accord. Re-treatment was satisfactory, and complete recovery without rebound had occurred at 21 months when steroids were finally withdrawn.

Patient *E.J.*'s disease relapsed after treatment for one year. Relapse is shown at 20 months, but no roentgenogram was taken in the interval. Relapse of active sarcoid lesions on withdrawing

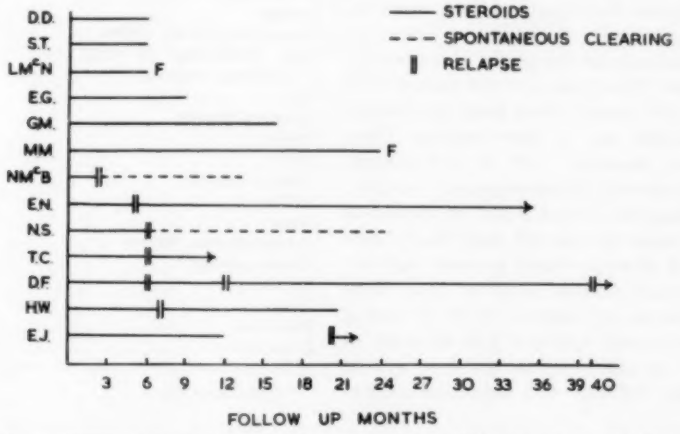

FIG. 64. Response to corticosteroids in 13 patients with pulmonary opacities.

TABLE 59

PULMONARY OPACITIES

THIRTY-THREE PATIENTS OBSERVED TO ROENTGENOGRAPHIC STABILITY

	Number	Per Cent
Spontaneous clearing	19	58
No treatment; progression to important fibrosis	3*	9
Clearing with steroids	7†	21
Continuing on steroids after relapse	4†	12

* Respiratory disability in one case
† Slight fibrosis in 2 cases

steroids is usually prompt, and it is virtually certain that relapse occurred earlier than is indicated here.

No relapse occurred in 6 patients after withdrawing steroids. In 3 patients, treatment was given for the relatively short period of 6 months without relapse. The others had treatment for 9 (*E.G.*), 16 (*G.M.*), and 24 months (*M.M.*).

In 2 patients (*L.McN.* and *M.M.*), in whom slight fibrosis remains, the sarcoid process had existed for some years before treatment, and, as steroids are believed to have only a suppressive role in sarcoidosis, it must be assumed that in these cases the giving of steroids accurately coincided with waning activity of the disease.

To summarize the fate of pulmonary opacities (table 59), 58 per cent showed spontaneous clearing. Three patients, who, for one reason or another, had no treatment, progressed to roentgenographically important fibrosis over periods from 5 to 7 years. In only one of these, however, is there any respiratory disability as judged by clinical assessment and the results of ventilatory function tests. Twenty-one per cent recovered on treatment with steroids. Four patients continue on steroids after one or more relapses. These patients have responded well to re-treatment, have now achieved roentgenographic stability, and their responses probably will be classed as satisfactory when the sarcoid state finally subsides. Two of these are likely to have slight residual pulmonary fibrosis. Thus far, then, there has been a satisfactory outcome in 79 per cent of cases of pulmonary opacities but, in point of fact, in only one untreated case has there been an unsatisfactory outcome with important impairment of respiratory function. In this series, re-treatment with steroids after relapse has generally met with as good a response as initial treatment. It should be mentioned that every patient treated with steroids in this series had coincident antituberculous chemotherapy, although it is now realized that this was probably superfluous.

The diversity of lesions in the miscellaneous group is indicated in table 60 and at the same time an indication is given of the frequency of involvement of the various tissues in the whole series. The cases of sarcoidosis which the chest physician sees naturally reflect his interests, and the figures given here cannot be taken to represent the true incidence of involvement of the various tissues in sarcoidosis.

There is not time to discuss the fate of miscellaneous lesions individually. I would like to say a word, however, about lesions involving the eye. There were 9 cases of iridocyclitis in the series. Most of these were referred by the eye department, and several patients had had treatment with local cortisone for up to 3 months, with only a limited effect. Treatment with systemic steroids had a dramatic effect in every case, often evident within 48 hours, and no patient has been left with any important visual

TABLE 60

TISSUES INVOLVED IN 100 CASES

	Number
Hilar lymph nodes	80
Lungs	44
Superficial lymph nodes	34
Skin (including 26 cases of erythema nodosum)	31
Eye	9
Salivary glands	7
Spleen	5
Liver	4
Cranial nerves	6
Kidney	3
Bone	3
Subcutaneous tissues	3
Nasal mucosa	2
Pituitary	2
Heart	2
Pancreas	1*
Bronchus	1

* Questionable

disturbance. The point we wish to make is that, in our view, eye involvement demands systemic steroids.

In 8 of the 20 cases of miscellaneous lesions in various combinations, the sarcoid process has pursued a chronic course with manifestations over periods of 4 to 15 years. Seventeen of the 20 patients have required treatment with steroids, and in 7 this is being continued after periods of 1 to 5 years. No patient with active manifestations of sarcoidosis has failed to respond to steroids, and this applies to the series in general.

EPIDEMIOLOGY OF SARCOIDOSIS IN JAPAN[1]

Preliminary Report

KEIZO NOBECHI

In 1921 Takeya (1), Professor of Dermatology, Tohoku University Medical School, reported the first 2 cases of sarcoidosis from Japan. Since that time, about 150 cases of this disease have been reported in Japanese medical journals. To comply with the request to report to the present Conference on the epidemiologic experience with sarcoidosis in Japan, the Provisional Committee for Epidemiological Survey on Sarcoidosis in Japan[2] was created in January, 1960. The primary purpose of this Committee was to collect pertinent information on every case of sarcoidosis ever diagnosed in Japan.

Materials and Methods

The Committee prepared two kinds of questionnaires, a screening questionnaire and a detailed questionnaire. The screening questionnaire was concerned with the identification of cases of sarcoidosis, regardless of the terminology conventionally used in the past for diagnosis. This initial questionnaire was distributed to 325 medical school clinics and to 458 other institutions, such as national hospitals, sanatoriums, and leading public and private hospitals. Detailed questionnaires, designed to elicit certain data deemed necessary for the epidemiologic study of sarcoidosis, were sent to those clinics and hospitals whose response to the screening questionnaire indicated the availability of records on such cases.

By the end of April, 1960, 94 confirmed cases of sarcoidosis were collected through careful review of completed questionnaires by a group of physicians with experience with sarcoidosis. Detailed questionnaires for 193 additional cases are being reviewed to confirm diagnoses. Since all questionnaires have not yet been returned, the total number of cases is expected to be still larger. The 94 confirmed cases will constitute the basic data for this preliminary report. However, upon completion of the study, a report based on all confirmed cases will be prepared.

Characteristics of the sample cases: Confirmation of the 94 sample cases in this preliminary report was based upon histopathologic, clinical, and immunologic findings. In 78 cases, histopathologic examinations were done, and all patients displayed the findings peculiar to sarcoidosis.

Observations

The sites of the lesions of the 94 cases are given in table 61. It is apparent from this table that in Japan the most common type of sarcoidosis is the pulmonary form, which is consistent with the present situation in other countries. Similar to American experience, not a single case of erythema nodosum was noticed in the present sample. However, this is not due to darkness of the skin, because in cases of collagenosis or Izumi fever (2, 3), the occurrence of erythema nodosum is quite frequently noticed.

Corticosteroids were administered in 52 instances, and in 42 (87.7 per cent) of these cases the therapy was considered effective. In more than 50 per cent, i.e., 27 of 52 cases, an outstanding improvement was noted. In contrast to this, in only 7 of 37 cases (approximately 19 per cent) treated with antituberculous drugs could the effect be considered satisfactory.

Among 72 cases examined hematologically, there were 20 cases of eosinophilia and 10 additional cases of other anomalies. As for the albumin-globulin ratio, 23 of 56 patients examined revealed hyperglobulinemia. Acceleration of the erythrocyte sedimentation rate was noticed in 35 of the 75 patients examined.

It was reported that 26 patients were cured

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Shigematsu, I., M.D. and M.P.H., Staff, Department of Epidemiology, Institute of Public Health.

Soda, T., M.D. and M.P.H., Vice-Director, Institute of Public Health.

TABLE 61
SITES OF LESIONS IN 94 CASES OF SARCOIDOSIS

Site	Cases	Per Cent of 94 Cases
Lung	54	57.4
Hilar lymph nodes	68	72.3
Other lymph nodes	42	44.6
Skin	34*	36.2
Eye	35	37.2
Parotid	5	5.3
Bone	8	8.5
Other organs	9	9.6

* No case of erythema nodosum

TABLE 62
PROGNOSIS OF CASES OF SARCOIDOSIS

Total	94
Cured	26
Improved	28
Unchanged	12
Worsened	5
Recrudescence	2
Deaths	2*
Unknown	19

* One died of heart sarcoidosis and the other of panmoniliasis

and the condition of 28 was improved. In 19 cases the prognosis was unknown; that is, 54 patients (72.0 per cent with records of known prognosis) exhibited improvement in due course, as seen in table 62.

The results of tuberculin testing in the sample cases are shown in table 63. Of 84 patients for whom the records of the test were reported, 68 (81.0 per cent) were tuberculin-negative. This is an outstanding finding when contrasted with the fact that the tuberculin reaction is positive in more than 90 per cent of a comparable age population. Furthermore, it may be seen in table 63 that of 28 patients whose tuberculin reaction was known to be positive before the onset of sarcoidosis, 14 patients (50 per cent) were tuberculin-negative when sarcoidosis was diagnosed.

Among the present cases, the Kveim test was carried out in 7 instances, and in 2 of these a positive reaction was obtained. In 71 instances, serologic tests for syphilis were made. However, all reacted negatively.

The characteristics enumerated above will serve to illustrate that in Japan we are dealing with the same disease as in America and Europe.

Chronologic trends in the frequency of cases, diagnostic terminology, and method of discovery: The chronologic trend in the frequency of reported cases of sarcoidosis, by the year in which they were diagnosed, is shown in table 64. During the twenty-five years following Takeya's 1921 report, until the termination of World War II, only 4 of the 94 sample cases were diagnosed. In the post-war ten-year period from 1946 through 1955, 26 cases were diagnosed; and during the last five years, the remainder of the cases, namely, 64, were given the diagnosis of sarcoidosis. The post-war experiences were further broken down into two-year periods, and the result is depicted in figure 65. These findings clearly illustrate that the general Japanese medical circle only very recently has become aware of the existence of sarcoidosis. However, their interest in this disease is apparently growing very

TABLE 63
RESULT OF TUBERCULIN TEST

Before Onset of Sarcoidosis	On Diagnosis as Sarcoidosis			
	Total	−	+	Unknown
Total	94	68	16	10
−	21	18	1	2
+	28	14	7	7
Unknown	45	36	8	1

− = tuberculin negative
+ = tuberculin positive

TABLE 64
CHRONOLOGIC TRENDS IN FREQUENCY OF CASES AND DIAGNOSTIC TERMINOLOGY BY YEAR OF DIAGNOSIS

Period	Diagnosis				
	Total	Boeck's Lupoid	Boeck's Sarcoid	Sarcoidosis	Others
Total	94	5	10	68	11
Pre-war 25 years (1921–1945)	4	3	0	0	1
Post-war 10 years (1946–1955)	26	2	5	14	5
Recent 5 years (1956–1960)	64	0	5	54	5

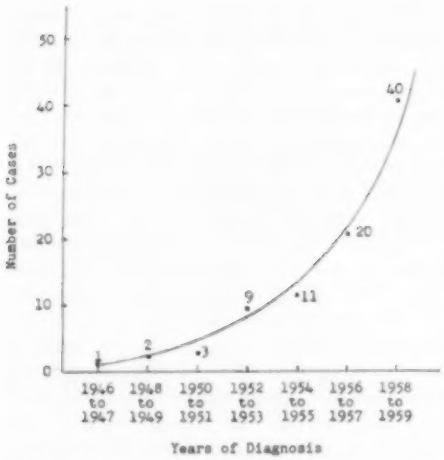

FIG. 65. The trends in frequency of discovery of cases of sarcoidosis in Japan during the years 1946 through 1959.

rapidly. Therefore, it seems quite logical to anticipate that the amount of data available for epidemiologic studies of this disease will be increased considerably in the near future.

For historical interest, the data showing the evolution of predominant diagnostic names for sarcoidosis is added in table 64. Following Takeya, who utilized the name "Boeck's lupoid" in his reports of 3 cases of sarcoidosis of the dermal type (a third was later added to the initial 2 cases), the same diagnostic name was still used by some clinicians in the post-war period. Utilization of the term "Boeck's sarcoid," as exemplified in the present *International List of Diseases and Causes of Deaths*, began to be adopted during the immediate post-war period and has extended into the recent period. However, during the post-war period the present international term "sarcoidosis" became predominant, and now the greater part of the cases are given this diagnostic name.

The chronologic trend in major causes leading to the discovery of sarcoidosis is also worth mentioning. As shown in table 65, in the pre-war period patients visiting doctors because of complaints with skin lesions led to the diagnosis of sarcoidosis. Although complaints with skin lesions, eye troubles, and other symptoms were still the predominant reasons for the diagnosis of sarcoidosis in the early post-war period, the number of cases "accidentally" discovered through routine physical and mass examinations became increasingly important. In the recent period the latter group has surpassed the former, especially the accidental discovery on mass physical examination, including fluoroscopy.

Sex and age distributions: The predominance of cases of sarcoidosis in the age group from twenty to twenty-nine years, as seen in table 66, is a striking finding. It reminds us of the age distribution of the Negro patients with this disease reported by Longcope (4). If this marked accumulation of sarcoidosis cases in the lower age group among the Negroes of the southeastern United States is governed by the epidemiologic rule, "epidemization precession" or "Durchseuchungspraezession" postulated by Gottstein (5) or, in other words, if the predominant distribution of sarcoidosis in the lower age group in Negroes is a result of the higher prevalence of this disease among Negroes, then a parallel situation may exist in Japan, namely, a higher prevalence of sarcoidosis may be expected among the Japanese.

TABLE 65

CHRONOLOGIC TREND IN MOMENTS OF DISCOVERY OF CASES

	Pre-War 25 Years (1921–1945)	Post-War 10 Years (1946–1955)	Recent 5 Years (1956–1960)
Total	4	24	66
Complaints: eye		5	7
Complaints: skin	3	5	8
Complaints: others		6	13
Mass examination		3	22
Other examination		1	5
Treating other diseases		4	8
Unknown	1		3

TABLE 66

AGE AT THE TIME OF DIAGNOSIS AND SEX DISTRIBUTION OF CASES OF SARCOIDOSIS

Age	Total	Male	Female
Total	94	51	43
0–9	0	0	0
10–19	9	4	5
20–29	47	32	15
30–39	15	5	10
40–49	13	4	9
50–59	9	6	3
More than 60	1	0	1

TABLE 67

GEOGRAPHIC DISTRIBUTION OF CASES OF SARCOIDOSIS BY RESIDENCE AT THE TIME OF DIAGNOSIS

District	Cases	Population*	Agricultural and Forestry Workers (15 Years and Older)†		
			Total	Agriculture	Forestry
Northern Japan					
Total	71	42,800,150	7,685,400	7,473,600	211,800
Hokkaido	2	4,773,087	714,300	670,800	43,500
Tohoku	15	9,334,442	2,391,100	2,313,600	77,500
Kanto	48	20,649,430	2,609,100	2,575,200	33,900
Hokuriku	6	2,741,363	572,500	552,700	19,800
Central	0	5,301,828	1,398,400	1,361,300	37,100
Southern Japan					
Total	23	46,475,379	7,695,700	7,382,200	313,500
Tokai	6	9,488,831	1,499,800	1,436,300	63,500
Kinki	10	12,811,830	1,238,900	1,182,400	56,500
Chugoku	3	6,992,008	1,466,200	1,404,500	61,700
Shikoku	2	4,245,243	944,600	891,500	53,100
Kyushu	2	12,937,467	2,546,200	2,467,500	78,700

* 1955 Japanese National Census

† Estimated number from 1 per cent sample of 1955 Japanese National Census

However, in the nationwide surveys of tuberculosis prevalence carried out by the Japanese Government in 1953 and 1958 with the cooperation of leading tuberculosis specialists, not a single case of sarcoidosis was detected in random samples of 50,000 and 70,000, respectively. This was true even though special attention was paid to this disease when questionable cases were scrutinized. As a result, it has been inferred that this disease has a low prevalence rate in Japan.

Mass physical examinations are strictly and extensively practiced in Japan under the Labor Standard and the School laws. The subjects of the former law are comparable, in respect to age, to the population prone to sarcoidosis. The high yield of sarcoidosis cases by means of mass physical examinations in recent years may be regarded as one of the major factors contributing to the accumulation of cases in the twenty- to twenty-nine-year age group. Thus, the observed age distribution is a social rather than a biologic phenomenon.

The age distribution of sarcoidosis discussed above was based upon the age at diagnosis. Later we will study the distribution of age at the time of onset of the disease.

TABLE 68

DISTRIBUTION OF CASES OF SARCOIDOSIS BY ECOLOGIC CONDITION OF RESIDENCE AT DIAGNOSIS

Area	Cases
Total	94
Urban	46
Rural	26
Mountain village	13
Coastal	6
Unknown	3

TABLE 69

OCCUPATIONAL DISTRIBUTION OF CASES OF SARCOIDOSIS AT DIAGNOSIS

Occupation	Case	Workers (15 years and Older)*	
		Population	Per Cent
Total	94	39,154,300	100.0
Agriculture	17	14,855,800	37.9
Forestry	0	525,300	1.3
Others	77	23,773,200	60.8

* Estimated number from 1 per cent sample of 1955 Japanese National Census

As for the sex distribution, a slight predominance of males is noticed in table 66. However, this is largely due to the exceptionally high prevalence in the 20- to 29-year-old group on the masculine side, and again this could be attributed to the high rate of discovery by mass examinations under the Labor Standard Law. Since the subjects are predominantly male factory workers, this may account for the decidedly high masculine prevalence in the age group concerned.

Geographic distribution: The distribution of cases, utilizing residence at the time of diagnosis, in the districts of Japan is displayed in table 67. If the country is divided into two areas by the Fuji-Hakone mountain range, the prevalence of sarcoidosis in the northern area is found to be almost three times as high as in the southern area. The total population, as well as the number of agricultural and forestry laborers, in these areas is very nearly the same. However, the predominance of sarcoidosis in northern Japan seems to be influenced by the high return of cases from the Kanto district, in which Tokyo City, with nine medical schools and leading hospitals or medical institutions, is located. This provides the north with a greater frequency of opportunities to discover cases. Therefore, it may be safer to wait for the results of further observations before stating definite conclusions concerning the geographic distribution of sarcoidosis in Japan.

The distribution of cases by the ecologic condition of residence at the time of diagnosis is set forth in table 68. In contrast to other areas of the world, the rural predominance of sarcoidosis could not be confirmed. In future studies, we will attempt to observe the correlation of patients with their residence before the onset of the disease.

Occupational distribution: The sample cases of sarcoidosis were tabulated by occupation, and the results obtained are shown in table 69. Unlike other countries, the tendency for predominance among farm workers could not be seen. Not a single case was uncovered among forestry workers. However, this might be the expected odds, since only 1.3 per cent of all workers are in forestry, unless a specific predominance in forestry workers prevails.

The apparently low prevalence of sarcoidosis, in spite of the fact that Japan is a noted pine country, and the geographic and occupational distributions so far disclosed do not support the pine pollen theory. However, the fact that Japanese pine trees are largely of a two-leaf type, whereas in the United States those of the five-leaf type predominate, should be taken into account. In this connection, it should be remembered that both types of trees are further classified into scores of subspecies.

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EPIDEMIOLOGY OF SARCOIDOSIS IN SWITZERLAND[1]

ERWIN A. UEHLINGER

Stimulated by the highly interesting observations of Dr. Cummings, Dr. G. Schonholzer and I initiated an inquiry into the geographic distribution of sarcoidosis in Switzerland from case material available in our own Armed Forces. In the years from 1940 to 1952, 120 cases of sarcoidosis were discovered in the Army. After exclusion of all doubtful cases, 108 cases remained to be evaluated. The organs chiefly involved were the tracheobronchial lymph nodes and the lungs. The so-called Löfgren syndrome was observed only six times.

With respect to the relationship between the occurrence of sarcoidosis and forest distribution, Switzerland may be divided into 3 regions: (*1*) the western region, comprising the foothills of the Jura range and wooded chiefly with conifers; (*2*) the plains region, centrally located and wooded with deciduous trees; and (*3*) the Alps, which has a coniferous zone at the snow boundary.

When the cases of sarcoidosis are plotted on a forest map, it may be seen that there is no relationship between the frequency of sarcoidosis and the distribution of conifer forests. The Jura region, especially, with its enormously rich forests, is almost free of sarcoidosis.

A comparison of the geographic distribution of sarcoidosis in relation to the rainfall distribution yields the following results: Regions rich in rainfall in Switzerland are the Alps and the Jura, whereas the plains region is relatively dry. An inverse relationship exists here between sarcoidosis and the amount of precipitation. In the dry plains region, which is also the most densely populated, sarcoidosis unquestionably occurs most frequently. The incidence of sarcoidosis is almost directly proportional to the population density (figure 66).

(Figure 66 on following page)

[1] From the Kantonsspital, Zurich, Pathologisches Institut der Universitat, Zurich, Switzerland.

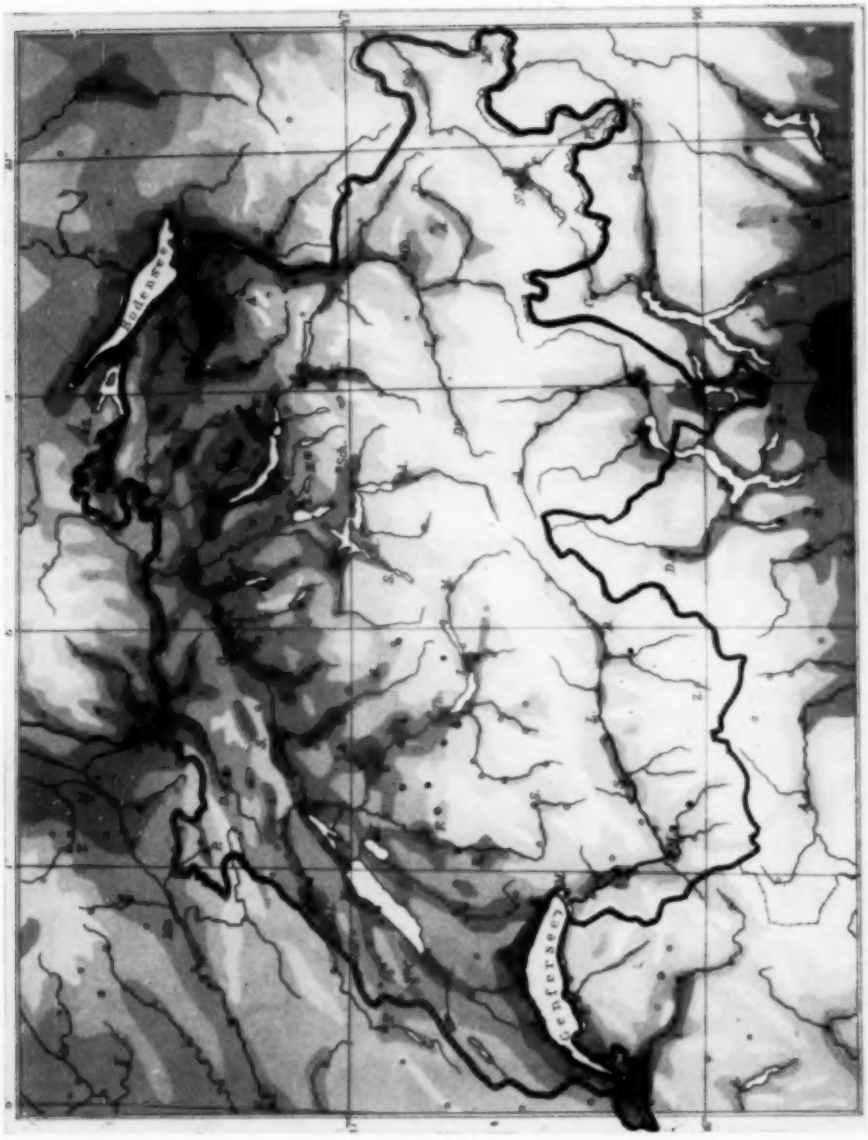

FIG. 66. Geographic distribution of cases of sarcoidosis in the Swiss Army in relation to the density of the population. The darkest fields have a density of 200 per sq. km.

EPIDEMIOLOGY OF SARCOIDOSIS IN URUGUAY AND OTHER COUNTRIES OF LATIN AMERICA[1]

PABLO PURRIEL AND EDUARDO NAVARRETE

Uruguay lies within the temperate zone of the southeastern coast of South America, between Brazil and the Argentine, and runs north to south in parallel 30° to 35° latitude south. Its area is 187,000 sq. km.

Of about 2,500,000 inhabitants, 1,000,000 live in Montevideo, which is the capital city. It is the country with the greatest proportion of its population concentrated in the capital. The population, mostly descended from Italian and Spanish and—in a minor proportion—from French and central Europeans, is predominantly white. A very small sector (10,000) has traces of Negro blood which may be traced back four or five generations.

The country's economic resources depend on cattle and sheep. The only export products are meat and wool. Ten per cent of the country is dedicated to agriculture. The principal industries are derived from livestock and agriculture, and the manufactured products are textiles.

Epidemiology of Sarcoidosis in Uruguay

Our first task is to reach an agreement on the essential requirements for the diagnosis of sarcoidosis in a patient. The criteria developed by the Conference on Sarcoidosis in 1948 in Washington and the National Academy of Sciences-National Research Council Subcommittee on Sarcoidosis in 1956 have been taken into account.

In 1939, for the first time, 2 cases were diagnosed in Uruguay. In 1942 and again in 1948, single cases were observed. Between 1949 and 1956 we were able to assemble 31 cases, which were published in *El Tórax*. Since then, 32 additional cases have been studied. From this we may infer that sarcoidosis, without being an important problem, appears more frequently in Uruguay than in the other South American countries.

Reasons for this may be multiple. One which carries weight is that in the past few years our doctors have had a better chance to study the illness. Another reason that must be taken into account is Uruguay's organization of mass roentgenographic examinations. Twenty-five per cent of the diagnosed cases have been discovered in this way.

In our clinic the first case was found in 1950, a date which I inevitably link with my stay in the United States when I made the happy acquaintance, both personal and scientific, of Doctors Israel and Sones. All of this has enabled us to delve deeper into the illness. Since then we not only search for it, but we acquaint others with the diagnostic procedures.

Among 50,000 patients registered at the Hospital de Clinicas "Dr. Manuel Quintela," where we have our medical service, 0.06 per cent were suffering from sarcoidosis.

The ages of patients studied on the service are as follows:

14 to 20 years old:	3 cases
21 to 30 years old:	9 cases
31 to 40 years old:	7 cases
41 to 50 years old:	10 cases
51 to 60 years old:	10 cases
61 to 70 years old:	1 case

There were no patients less than 14 or more than 67 years of age. Surveys made in the children's clinics indicate that there is no knowledge of sarcoidosis among children.

We have observed very little difference in the frequency of cases in the sexes. The percentages in men and women coincide.

In figure 67 we have given the location of the patients. Attention is drawn to the fact that 55 lived in Montevideo and only 12 in the rural zones. This inverts the relation accepted by most writers who emphasize, when dwelling upon the epidemiology of the illness, that it originates more often in the rural areas. We limit ourselves to pointing out the fact, without intending to give it a conclusive interpretation. Reasons to account for this could be the insufficient acquaintance of rural doctors with the illness and the scarcity of technical equipment for diagnosis in these areas.

In recent years, the importance of pollen from pine trees in the etiology of the illness has been emphasized. Several epidemiologic and experimental papers have been written on the subject.

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FIG. 67. Epidemiology of sarcoidosis in Uruguay.

Uruguay's climate and geographic position make it a favorable place for the cultivation of pine trees. All along the southeastern beaches there are extensive pine tree plantations which stretch out for about 150 km. and are, in some places, 5 km. wide. They are on the shores of the River Plate and the Atlantic Ocean, in the states of Montevideo, Canelones, Maldonado, and Rocha. There also are forests of varied species on the banks of the Black River. Uruguay's plantations are more than fifty years old, which makes our country, in proportion to its size, the one which probably has more pine trees than any other in Latin America. In the rest of the country there are only isolated specimens. The majority of the pine trees are of the variety known as "pinus maritimus" or "pinus pinnaster."

In Montevideo, where 80 per cent of the patients with sarcoidosis lived, there are woods of pine trees in the east of the city. Only one of our patients lived there. The rest had been living in zones at a considerable distance from the pine tree area. Of the 12 patients from the rural zones, only one lived in the pine area. The rest resided at long distances from it. We admit that pollen may travel a long way, but our attention has been drawn to the lack of connection between the location of the forests and the patient's place of residence.

As is obvious, it is impossible to arrive at any positive conclusions on pollen sensitization and sarcoidosis in Uruguay.

With respect to the lumber industry, sarcoidosis has not been found among its workers. We call attention to the fact that Uruguay produces very little lumber, and must therefore import the

greater part of that which is consumed by the industries.

Sarcoidosis and mass examinations: Mass roentgenography and BCG vaccinations are carried out in Uruguay with a fleet of fully equipped vehicles. Fifteen per cent of the total population is examined yearly. Because children are vaccinated at birth in most cases, and are revaccinated before they are five years old, the percentage of allergic reactions to tuberculin does not allow us to establish a prevalence rate. However, at the age of five, 45 per cent of the children are positive to tuberculin and, between twenty-six and thirty years of age, 81.4 per cent are positive. Of every 100 people examined, 0.3 are found with roentgenographic shadows, indicating possible active tuberculous lesions.

In Uruguay in the last fifteen years, 6,000,000 roentgenograms have been obtained. If the number of bacillary patients found by mass examination is compared with the number of patients with sarcoidosis, it may be seen that the relation between the two is far from approaching the one found in other countries, like Sweden. Nevertheless, it is possible that this method of prophylactic examination partially accounts for the greater frequency with which sarcoidosis is found in Uruguay as compared with that in other South American countries. It has already been said that 25 per cent of the cases studied were discovered in this way. This is in accordance with the manner in which, from the symptomatic point of view, sarcoidosis appears. Patients may have very mild symptoms, or none at all, or they may appear with a varied clinical picture. The first two groups may be diagnosed only through mass examination and, according to our statistics, they constitute 25 per cent of the patients which were studied.

Histoplasmosis: As to the connection between histoplasmosis and sarcoidosis, we must make it clear that this fungal disease has not yet been properly studied by us. There are insufficient epidemiologic data and only a few clinical cases which are correctly diagnosed.

In 1947, intradermic injections of histoplasmin were made on 1,189 persons of different environments and ages. The positivity index was 8.9 per cent: 3.32 per cent for women and 14.67 per cent for men. There is no record of skin tests and lung calcifications. We have just finished a checkup of 100 patients with different diseases hospitalized in our clinic. Sixteen per cent of them had positive reactions to histoplasmin skin tests.

From the clinical point of view, 15 cases have been diagnosed. All of the patients had important oropharyngeal injuries accompanied by dermic and pulmonary lesions. At present we are planning a vast epidemiologic study because of the scarceness of data in our country concerning this mycosis.

Blastomycosis: The same can be stated in our reports on blastomycosis. There are, at present, only 11 well-documented cases. This lack of observed cases contrasts sharply with the large number found in Brazil. This point also needs further investigation.

Berylliosis: In Uruguay, there is little possibility of intoxication by beryllium, but one case was studied by us years ago. Almost all of these mycoses are in patients who reside in rural zones.

Sarcoidosis Epidemiology in Latin America

South America has 125,000,000 inhabitants, and more than half live in Brazil and Argentina. We will describe the Brazilian population. This country is the largest in South America, and within its borders lives the greater part of the Negro population. Brazil has 52,000,000 inhabitants, 32,000,000 of which are white; 5,600,000 are Negroes whose ancestors came to Brazil from Africa centuries ago; 14,000,000 are mulattoes, and 300,000 are of Asian descent. There is no knowledge of the Indians who live in the Amazon forests. Brazil is the country in South America with the greatest percentage of Negroes, 10 per cent Negroes and 26 per cent mulattoes. In other countries such as Colombia and Venezuela, there are also significant numbers of Negroes within the population.

The epidemiologic data on sarcoidosis in Latin America are very difficult to obtain. However, for the purpose of making an epidemiologic map, we resorted to personal inquiry and bibliographic research. The former was carried out by correspondence with the leading specialists on diseases of the chest in each country. Replies were limited in number and shed little light on the subject, because our correspondents limited their information to the number of cases, omitting to point out characteristic symptoms and diagnostic criteria. In the bibliographic investigation, it was possible, in most cases, to learn how cases had been studied and to form an opinion on the authenticity of the diagnoses. It may be possible that other cases exist besides the ones shown here. We have direct

FIG. 68. Number of cases of sarcoidosis in Central and South America.

knowledge of Uruguayan cases, but it is not possible for us to be sure of the exact number of cases in other South American countries.

In figure 68, the recorded cases are shown by the solid-line square; the cases known through personal correspondence (upon request) are shown in the dotted-line square. In countries such as Colombia, which has 12,500,000 people, Equador with 3,500,000, and Venezuela with 6,000,000, we have been unable to find any report on sarcoidosis. Chile, with a population of 6,500,000, has only 2 published cases; and Bolivia, with 3,200,000, has only one. According to our information, there are 63 cases in Brazil and 57 in the Argentine.

As to the date of appearance of the South American cases, between 1934 and 1949, it was possible to find only 14 cases. From 1950 to 1960 we collected 180 cases. It is possible that the greater frequency of reported cases in the last ten years is due to an increased awareness of the disease and to diagnostic methods.

We have information on the existence of 194 cases among the 125,000,000 inhabitants of South America. Of this number, 67 are Uruguayan cases. Therefore, it is possible to say that 34 per cent of known cases in South America are in Uruguay, which represents only 2 per cent of this continent's population.

About the epidemiology of sarcoidosis of Cen-

tral America we can say only that in our investigation it was not possible to find bibliographic reference to sarcoidosis in Costa Rica, Guatemala, Haiti, Nicaragua, El Salvador, or the Republic of Dominico. We have information that one paper from Cuba and another from Panama have been published, but it was not possible to obtain these. There is one published work with 5 cases from Honduras. We have no information from Mexico.

As for pine forests in Latin America, there are large expanses of them in Argentina and in Chile. In the latter country, we know of only 2 cases of sarcoidosis.

This general information allows us to draw some conclusions, without assuming that we have exhausted the subject:

Uruguay is the country where there appears to have been more sarcoidosis. A notable fact is that most cases were found in the urban zones.

The clinical features, evolution, and the death rate of sarcoidosis in Uruguay is the same as in other parts of the world.

There seems to exist no connection whatever between the location of pine forests and the predominance of the illness in Uruguay or in the rest of South America.

Sarcoidosis seems not to be prevalent among the great numbers of Negroes and mulattoes who live in Brazil. Our attention is drawn to the different epidemiology of the illness in certain zones of the United States, Sweden, and South America.

With the exception of Uruguay, we cannot guarantee the exact figures given for existing cases.

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SARCOIDOSIS IN SOUTH AFRICA[1]

B. VAN LINGEN

Sarcoidosis in South Africa is a comparatively rare disease. Only five cases have been reported in the South African medical literature, and two of these patients were born overseas. No autopsy record of a case of sarcoidosis could be found in the pathology departments of the five teaching hospitals of South Africa.

The material analyzed in this study was obtained from the above-mentioned teaching hospitals, and in each case the clinical records and histologic sections were consistent with a diagnosis of sarcoidosis.

In the European population (total 3,500,000), 18 patients with sarcoidosis were found, 4 of whom were born overseas and 14 in South Africa. The places of birth and residence could not be traced in 9 of the 14 subjects who were born locally. In those from whom this information was available, 3 patients had been born and had lived in close proximity to pine plantations, and 2 had not. Eight of the subjects were female, with an average age of forty-five years, and 10 were male, with an average age of forty-three years.

In the African population (Negro), 30 cases were found in a total population of 10,500,000. Sixteen of these patients have been traced: 10 lived during the early part of their lives in close proximity to pine forests, 3 did not, and in 3 patients the association was doubtful in that their early lives had been spent within twenty to thirty miles of large pine plantations. It should be stressed that those who were considered to have an association with pine lived in intimate contact with this type of plantation. Of the total patients, 15 were female, with an average age of thirty-nine years (range, twenty-two to seventy years), and 17 were male, with an average age of twenty-seven years (range, eight to forty years). Two subjects with sarcoidosis were Indian; one had and the other had not lived close to pine trees.

Pine plantations in South Africa have been developed for industrial purposes, and the tree is not indigenous (1). This has resulted in their being grown in limited locations along the southeastern seaboard of South Africa and in the eastern Transvaal and Swaziland. The total area under pine is about 1,200 square miles in a country of about 470,000 square miles. This localization of pine to certain limited regions lends itself to the testing of the pine-pollen hypothesis far more accurately than would be possible in countries where the tree is commonly found and widely distributed.

Unfortunately, it has not been possible to ascertain the true incidence of this disease in South Africa. In many of the patients found, it was not possible to obtain the places of birth and residence during early life. However, in the African series, a high percentage of patients with sarcoidosis were found to have been intimately associated with pine plantations from birth through adolescence. This association is remarkable in the sense that the area under pine is limited and the majority of the traced cases come from such areas, while the general distribution of the African population in South Africa suggests that this finding is significant.

The study would appear to indicate that the pine-pollen hypothesis has merit and that further attempts should be made to trace all available cases in South Africa to further test its validity. The distribution of pine in South Africa is sufficiently limited and the African population sufficiently static during early life to make a statistical comparison of sarcoidosis and pine forestation a worthwhile project.

No distinct difference between the incidence of sarcoidosis in the African and European populations in South Africa could be found. This contrasts with the increased frequency found in the American Negro. On the other hand, the disease appears to attack the African earlier than the European, a finding similar to that for the Negro in America.

[1] From the Cardiac Clinic, General Hospital, Johannesburg, South Africa.

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EPIDEMIOLOGY OF SARCOIDOSIS IN THE UNITED STATES[1]

EDWARD DUNNER AND JOHN H. WILLIAMS, JR.

This afternoon you have listened to a series of papers on the same general subject, "The Epidemiology of Sarcoidosis." Since this is the ninth and final paper in the series, I think it is appropriate to repeat a statement attributed to Dr. R. Keith Cannan: "Science does not fear duplication of effort but encourages it until it has been shown that new information has been confirmed to the point of becoming established truth. In the search for a single answer, many avenues must be explored and many explorers are needed."

Before mentioning the avenues which we have explored in the Veterans Administration, I should like to acknowledge the contributions of the explorers in our particular study—our Chief Medical Director, the Moderator of today's session, the Chairman and study unit representatives of the Veterans Administration–Army Cooperative Study of Sarcoidosis, and the consultants (several of whom are represented here today). I think it is fair to say that in recent years this group has succeeded in arousing considerable interest in sarcoidosis.

Since our experience in the epidemiology of sarcoidosis in the United States has been confined mainly to male war veterans, this factor should be borne in mind in interpreting the results of our studies. A roster has been kept of all veterans discharged from Veterans Administration hospitals with a diagnosis of sarcoidosis during the years 1949 to 1957, inclusive—approximately 2,000 patients. It became evident that, when one is reviewing a disease as nebulous as sarcoidosis can be, there are going to be differences in diagnoses from one hospital to another. There are bound to be some rather dubious cases included in the statistics. In fact, of almost 300 clinical records selected for review, 10 per cent were not considered to have sarcoidosis. In about 75 per cent of the 300 cases, the diagnosis included a biopsy or examination of material obtained at autopsy. It was interesting to note the high percentage of patients in whom biopsy was performed due to the difficulty in confirming a clinical diagnosis of sarcoidosis.

The occupations of some 500 veterans with sarcoidosis, as reported on the record of hospitalization, were compared with the occupations of a control group. In this latter group, occupations as reported for a single day census of admissions to the Veterans Administration hospitals were listed. There were some minor differences noted between the two predominantly male groups. Among specific occupations, there were more post office workers and mechanics among the veterans with sarcoidosis. In general, however, there was little difference from an occupational standpoint between patients admitted for sarcoidosis and patients admitted for other conditions. Obviously, this is subject to the criticism that a single occupation does not give the complete vocational history. However, one can postulate that if occupation was the important factor in sarcoidosis this would become evident, regardless of the point at which one decided to take a cross-section for review. This seems to be a reasonable view since, with most occupational diseases, the occupations of all of the patients prior to hospital admission would not all be related to the disease, but their occupations certainly would not be similar to those of a random group of patients.

In a different study, a comparison was made to discover whether the disease was more prevalent among Navy than Army veterans. The results were negative. An analysis also was made of the birthplaces of these veterans. This revealed, as frequently has been reported, that the prevalence of sarcoidosis is somewhat higher in rural than in urban communities. This is particularly true in the southeastern states where there are a number of small communities in which more than one sarcoid patient was born.

A look at the industry of some fifty cities and towns with a higher-than-average prevalence of sarcoidosis showed that twice as many of these communities had lumbering as a principal industry than did a random group of cities and towns in the country as a whole. This proves nothing, but it is worthy of note that a similar statement could not be made about other industries. A sample of 20 patients with sarcoidosis was selected and matched with a control group

[1] From the Department of Medicine and Surgery, Veterans Administration, Washington, D. C.

consisting of veterans of the same race, born in the same county, in approximately the same year. Social service workers then asked these 40 veterans a series of prepared questions relating to their contact with wood. The group with sarcoidosis had more contact, but not as much as might have been anticipated. The findings were inconclusive enough to make the likelihood of a direct relationship between lumbering and sarcoidosis rather remote.

Since one of the major findings of the Veterans Administration record study is the location of certain areas of higher prevalence of sarcoidosis, visits were made to a few of the so-called high prevalence areas. The impression was obtained that these areas share a somewhat similar ecology. Additionally, in the few instances in which it was possible to check the areas designated as endemic against adjacent areas designated as nonendemic, it was discovered that there were obvious differences in ecology as related to the soil and the type of growth it supports, especially trees. This technique of delineating areas of high prevalence of disease from Veterans Administration records, especially the clustering of counties into what seemed to be areas of high prevalence, has since been used for other conditions, e.g., multiple sclerosis, chronic ulcerative colitis, Paget's disease, and renal calculi.

It has been most difficult to determine the true incidence or prevalence of sarcoidosis since most reports in the literature deal with small numbers of cases usually seen in hospitals situated in large cities. Furthermore, many asymptomatic cases never come to the attention of a physician. Obviously, its true incidence is much higher than currently suspected. One of the peculiarities of the Veterans Administration system is a lack of knowledge of the population it treats. The total number of veterans is known, but no one knows what proportion seek assistance from the Veterans Administration for a specific disease. Certain parameters are known, such as the proportion of total patients that come from each state, the percentage of patients in each age group, et cetera. It is for this reason that we used comparative rates. In other words, one can say that the relative rate of sarcoidosis is ten to fifteen times higher among male Negroes than whites, but the absolute prevalence of sarcoidosis is not known. The minimal prevalence of sarcoidosis among World War II veterans is at least one per 100,000 on the basis of the many veterans who have been hospitalized in Veterans Administration hospitals for the disease.

Likewise, it is very difficult to draw many conclusions about age at onset of the disease. It would appear that the hospitalization of a person with sarcoidosis might occur as long as five to eight years after exposure. This estimate is partially based on the length of time that elapsed before hospitalization of a few patients after they moved away from an endemic area. Actually, the problem of duration of incubation period has not as yet been investigated as thoroughly as it should. At least two avenues of investigation are open. The first is the further study of persons who have moved from endemic to nonendemic areas, or vice versa. The second is the investigation of the dates of trauma correlated with the development of local sarcoid lesions.

Even so, it appears that sarcoidosis is a disease of the young, since only 23 per cent of the whites and 15 per cent of the Negroes were more than forty years of age when admitted to the hospital. There is ample evidence that, on the average, Negro veterans were younger when first admitted to Veterans Administration hospitals than were white veterans. Approximately 20 per cent of the Negro veterans were less than twenty-five years old, and 50 per cent less than thirty, when first admitted. About 10 per cent of the white veterans were younger than twenty-five. Holding race constant, no dramatic differences were found between age at admission and place of birth. This was done on a sectional basis, i.e., New England as compared with the southeastern or the Middle Atlantic states.

We thus are concerned with a disease which: (*1*) is more prevalent in the United States among Negroes, (*2*) is more prevalent among individuals less than thirty years of age, (*3*) is more prevalent in the New England, southern, and north-central states than it is elsewhere in the country, (*4*) in general, is more prevalent in the East than in the West, (*5*) apparently bears little relationship to occupation, and (*6*) does not seem to appear in outbreaks or epidemics.

One might conjecture that if sarcoidosis is caused by a certain agent, then this agent exists to a greater degree in some areas than in others. It does not seem to exist to any degree in the large sections of farmland of Iowa or Nebraska. It is within the realm of possibility that these differences are caused by a variation in host response. This may be the cause of the wide discrepancy

between rates of sarcoidosis among whites and Negroes in the United States. If the hypothesis of choice is that there is some outside cause, then it would be reasonable to assume that, based on a relative distribution of sarcoidosis, there should be an accompanying distribution of the causative agent. Admittedly, this has been the choice of the Veterans Administration study group.

There is no doubt that the geographic distribution of the birthplaces of veterans with diagnoses of sarcoidosis is unusual. Analyses of the Veterans Administration material showed that at least three areas of high prevalence of sarcoidosis exist in this country. These areas are in the South Atlantic, New England, and the North Central states. This is true whether one takes place of birth or place of residence at time of hospitalization. These findings not only confirm the geographic distribution reported by Ransmeier and Michael and his associates, but extend the distribution pattern of the disease to areas of the United States in which the disease was not found to be endemic by these authors.

A question arose as to whether the newer defined endemic areas of the New England and north-central states represent hitherto unsuspected foci of sarcoidosis, or whether they represent those veterans who contracted sarcoidosis while serving in military camps located in the Southeast. This was ruled out by a tabulation of training sites for veterans from Iowa, a nonendemic area, which showed that the majority also had trained in the South. These findings led us to believe that the three endemic areas are true sites of high prevalence of sarcoidosis.

Further studies suggested that some aspect of the eastern forest distribution in the United States might be an important environmental factor, rather than solely the soil distribution formerly postulated to be responsible for the geographic concentration of the disease. There are many problems in approaching a relationship between sarcoidosis and forest density. The characterization of forest types is an oversimplification since most stands are of a mixed variety. We are confronted with using the percentage of land in forests as an estimate of relative exposure. Nevertheless, a series of analyses were done within about a dozen states according to the percentage of land in a forest and the predominant type of tree.

From data furnished by the Forest Service of the United States Department of Agriculture it was possible to divide certain states into three or four subdivisions, based on type and density of forest. The population of these subdivisions by race was obtained from census figures for the year 1920. Based on these population figures, relative rates of sarcoidosis were computed, using the number of Veterans Administration patients as the numerators.

The results were interesting. As the definitions progressively became more specific and we stopped considering trees and began to consider species, the better the material seemed to fit. While, in general, the comparisons between states were consistent, an exception was noted. The high prevalence area in northern Alabama and southern Tennessee is not located in what the Forest Service describes as a predominantly pine area. Quite often the exception proves the rule, and this exception offers a good possibility for checking the pine hypothesis. If it is found that this area contains local stands of pine in close proximity to the sarcoid cases, it would strengthen the hypotheses. On the other hand, if the pine relationship does not hold true in these areas, an investigation of this area has a better chance of uncovering a new lead than a similar investigation of other areas. This remains to be done.

Another interesting finding of this phase of the study was the fact that in various states there was agreement on relative rates according to type of pine. This was all the more intriguing because of our belief that a causative agent should commonly exist in the United States and in the Scandinavian countries, the cradle of sarcoidosis. The comparative rates of sarcoidosis in those states with multiple-type forests were found to be lowest in the areas with predominantly hardwood stands and highest in areas with predominantly shortleaf, pitch, or loblolly pine. Areas of predominant longleaf, slash, or Virginia pine were between these two. The consistency of the rates for a number of states leads us to place some credence in the findings. Additionally, an investigation of the predominant tree types in counties designated as having a higher than normal rate of sarcoidosis yielded substantially the same results.

Admittedly, there are many relationships between the existence of pine stands of a particular type and the remainder of the flora and fauna of the area. However, the successful use of the prevalence of a subspecies of a tree to delineate the

prevalence of sarcoidosis in a series of independent trials for various states seems strongly to indicate some relationship between ecology and the prevalence of sarcoidosis.

Exactly what the relationship is remains an enigma. As previously indicated, a fruitful source to investigate exists among those cases which do not fit the hypothesis. A cooperative study of sarcoidosis in children might shed considerable light on the etiology and incubation period of sarcoidosis since fewer false leads would be encountered. The Veterans Administration study tells us nothing about the relationship between sarcoidosis and females, but other reports state that females are more frequently affected. This fact, in itself, makes it difficult to envision any relationship between occupation and sarcoidosis. It would appear, then, that what we are seeking as the etiologic agent of sarcoidosis is present in most parts of the eastern United States, exists in a lesser degree or not at all in other sections of the country, is either in greater abundance in some rather well-defined areas or is more accessible to the people of such areas, and is common in the endemic areas of the United States and the Scandinavian countries. Additionally, certain evidence indicates that the availability of the agent is relatively constant in regard to time and place.

Discussion

Dr. Cummings: We are now ready to receive your questions and comments. We welcome your free discussion. If there are any representatives from parts of the world who have not been heard from formally, you are invited to speak at this time.

Dr. Siltzbach: I should like to make a few comments about sarcoidosis among the Puerto Rican-born population living in the East Harlem area of New York City. Sarcoidosis has not been especially frequently noted in Puerto Rico itself, and yet about 15 per cent of the patients on the Mount Sinai roster were born in Puerto Rico. Some of these patients have recently migrated from the island, and others have been in New York City for as long as a quarter of a century. As I stated previously, the erythema nodosum form of onset among the women of Puerto Rican origin is particularly noteworthy. Erythema nodosum with hilar nodes has been noted among recent arrivals in New York City, as well as among those who have lived in New York City for many years without having returned to visit Puerto Rico. We have recently begun a Nickerson-Kveim testing program in San Juan, and cases of sarcoidosis are being uncovered slowly. We still do not have enough female patients in the study group there.

We also have on our roster at the Mount Sinai Hospital cases of sarcoidosis among patients who were born in Barbados, Jamaica, and Trinidad. These patients are all Negro migrants to New York. Another of our cases stemmed from Dutch Guiana and, for Dr. Purriel's information, I have seen 2 patients from Colombia (both Spanish) on whom I was able to make the diagnosis of sarcoidosis. Another patient came from Venezuela, and Dr. Purriel's map can be amplified to this slight degree. Dr. Cummings, I note that no data were presented from Norway or New Zealand, and I shall be glad to give you that information as it appears in the literature. In the Norweigian armed forces, where 300,000 males were examined by mass roentgenography in 1952, the rate of sarcoidosis was 11 per 100,000. The rate for open tuberculosis in the same survey was 139 per 100,000. In New Zealand, mass surveys were made between 1952 and 1957, and a rate of 19 per 100,000 was found for sarcoidosis. The tuberculosis rate was 170 per 100,000. Only one Maori was found to have sarcoidosis. In the city of Amsterdam, the rate for sarcoidosis discovered on surveying 401,000 white inhabitants between the years 1954–1957 was 9 per 100,000, similar to the rate for New York City whites. The tuberculosis rate was 45 per 100,000. This represents a 100 per cent decrease in the prevalence rate for tuberculosis since the survey made in Amsterdam in 1951 to 1954.

Dr. Cummings: Are there any other reports of prevalence or incidence figures?

Dr. Lebacq: I have some cases to report from Belgium. I live in the southern part of Belgium where the coal mines are located. I do not believe, however, that coal has anything to do with the etiology of the disease because there are 120 cases in the Luvant, which is in the Flemish part of the country, where the people are agricultural workers. There is not a single case—or at least none has been reported—in the only region of Belgium where there are pine plantations, the region that is called the Arden.

Most patients are hospital cases, meaning that they are old or chronic, such as you have here in the United States. I have no exact statistics. I collected a case in Luvant, in the southern part of the country. No general study has been done in Belgium up to now. It may be that by the next conference I can bring such statistics as are now lacking.

Dr. Cummings: Thank you. Are there any other places to be heard from? Are there any specific comments or questions for the essayists?

Dr. Dublin: I would like to address a question

to Dr. McCuiston on the Florida study. I noticed that he had divided the study area into segments, in which he took pains to identify the pine forest areas, but he made no effort whatsoever to report on the possible association of the cases of sarcoidosis with either the total population or major population groups in these geographic zones. It would seem to me that there might well be an unequal distribution of white and Negro populations in these areas. I wonder if he would fill in this missing information.

DR. MCCUISTON: You are absolutely right; there is an unequal distribution of Negroes in the state of Florida. Although I cannot give you any exact figures on this, in the northern parts of Florida (primarily lumbering sections) there are more Negroes in proportion to whites than there are in the central and southern sections. In the central section, which is primarily agricultural (and this includes citrus groves), there are quite a few Negroes. However, the range is not marked, varying from about 25 per cent Negroes in the northwestern section to about 15 per cent in the southeastern section, without any correlation, from county to county, with the incidence of sarcoidosis.

DR. JAMES: In his elegant studies, Dr. McCuiston showed that pine pollen skin-test reactions were less commonly positive in patients with sarcoidosis than in control subjects. This assumes a depression analogous to that observed with the tuberculin test and other delayed skin tests. This is a reasonable assumption, but we cannot be certain. The point could be clarified by performing studies using pine pollen in oil as a depot pine pollen test. When this is done with tuberculin, a degree of tuberculin hypersensitivity is revealed in sarcoidosis which would not have been elicited by the conventional Mantoux test. If patients have negative Mantoux tests and positive depot tuberculin tests, it implies depression of the Mantoux test because of immunologic upset. This may be due to deficiency of cellular antibodies. It would be interesting to observe whether, in sarcoidosis, negative pine pollen tests are associated with positive depot pine pollen tests. Until we know this, it is difficult to interpret the significance of negative pine pollen tests in sarcoidosis.

DR. CHASE: I have one question for Dr. Purriel. I did not follow what he had to say about the distribution of Negroes with sarcoidosis in South America. I would like to inquire as to their economic status there. Negroes can be considered from several points of view. One is their hereditary background, which can be different, perhaps making them more susceptible to acquiring sarcoidosis; again, the disease might be associated with the economic status of Negroes. I wonder if you could tell us about the economic status of Negroes in South America, and perhaps say more about the geographical distribution of Negroes in those countries.

DR. PURRIEL: The only country that has an accountable number of Negroes is Brazil. Economic conditions are very poor throughout the country.

DR. CUMMINGS: I would like to ask Dr. Comstock a question. Could he describe the clay-eating habits a bit more precisely for some of us who are not familiar with this phenomenon? Is the clay actually ingested? How often is it eaten? Is it chewed? What are the amounts involved? What information do you have on that, Dr. Comstock?

DR. COMSTOCK: In our questionnaire we did not ask for details of how the clay was eaten. We did ask how often and at what period in life this was done. Half of our clay-eaters stated that they ate clay only during pregnancy. But this concentration during pregnancy may be more apparent than real. Folklore has it that the baby is benefited when the mother eats clay, and the practice may therefore seem more acceptable during pregnancy. About a quarter of those who admitted clay-eating said that they did so only during childhood. Nearly all of the clay-eaters expressed a preference for white clay. We got the impression that the subjects generally obtained their own clay from some spot where it was not contaminated by other material, and that the clay was baked prior to ingestion.

DR. HARDY: I want to compliment Dr. Comstock. This is the kind of study that I believe is important. As suggested by this study, I wonder if, rather than looking for different single causes of sarcoidosis, we should not be interested in a combination of factors affecting the patient prior to symptomatic disease. His finding that pregnancy is an important factor in sarcoidosis recalls our observations in beryllium disease, in which it was striking that a number of women who became actively ill with beryllium disease did so in the postpartum period. Does this physiologic phenomenon act in some fashion to trigger in a harmful fashion the burden of beryllium which, for a long period after the last beryllium exposure, has been harmless?

I should like to address to Dr. Dunner a hope that he will not give up recording occupational histories because of the delay in onset of industrial illness of many causes. Many valuable clues to etiology may be lost if such data are lacking in large groups.

DR. CUMMINGS: I wonder if I might ask Dr. Sartwell or Dr. Buck if they would be willing to tell us about a study that we understand is going on in Baltimore, which I think would be pertinent to the discussion.

DR. BUCK: With respect to Dr. Comstock's interesting observations on clay-eating, I would like to report the results of our controlled sarcoidosis family study.

In interviews, 13 of our 62 sarcoidosis cases and 13 of their matched control partners gave a history of pica. The term "pica" as used in this study included the eating of any or all of the following four types of substances: clay, earth, chalk, and plaster. The inaccessibility of a preferred substance, such as clay, could have led some of the many patients and controls who had migrated to Baltimore from smaller towns and villages in southern states to use starch as a substitute, if their craving for unusual "foodstuffs" persisted or reappeared. For this reason, questions concerning the eating of laundry starch were asked separately. No differences were found between our patients and controls, either for clay or starch alone or for all of the substances comprised in the term "pica." More women than men stated that they had eaten laundry starch or the substances included under "pica."

In another part of the study the hypothesis of a familial aggregation of sarcoidosis was examined. Whereas multiple cases of sarcoidosis were found in 5 of the 62 families of the patients, no case was detected among the 62 families of the controls, although the same diagnostic efforts were made.

To obtain clues as to whether the low prevalence of tuberculin and tuberculin-like skin reactions in sarcoidosis cases is due to a familial, constitutional factor leading to a suppression of these reactions, or whether it is the result of direct interference of their disease with the immune mechanism responsible for delayed skin reactions, tests with tuberculin and *Candida albicans* antigen were done on the patients, their matched controls, and the first-degree relatives of the patients and controls. The prevalence of skin reactions to these two antigens was found to be similar in the controls and their first-degree relatives as well as in those of the patients. Only the sarcoidosis patients themselves had a low prevalence of skin reactions to tuberculin and *Candida albicans* antigen. In addition, a general suppression factor could be computed showing that there was no preferred suppression of tuberculin reactions.

No clues were obtained to support the hypothesis that suppression of delayed skin reactions is the result of constitutional factors more frequently present in first-degree relatives of sarcoidosis patients.

DR. LÖFGREN: I think it is very important to look for various pathogenic factors to explain the occurrence of sarcoidosis. One pathogenic factor, pregnancy, is well known. It was found in our material that hilar adenopathy very often occurs in connection with lactation or—more precisely—when lactation is just finishing. Thus, in one-third of the erythema nodosum cases in females, the skin eruption appeared in such a connection.

Regarding the pathogenic aspect, I would like to make a comparison between tuberculosis and sarcoidosis. I think every phthisiologist has the experience that social disadvantage plays an important role in the pathogenesis of tuberculosis; chronic alcoholism, for example, is fairly common among these patients. When considering my sarcoidosis material of more than 500 patients, I must say that these patients belong to another social class, and I cannot remember one single sarcoidosis patient who is a member of an "alcoholic club."

In other words, social disadvantage is not a pathogenic factor in sarcoidosis as it is in tuberculosis. Instead, perhaps the hormonal influences are of greater importance in sarcoidosis than in tuberculosis.

DR. ISRAEL: Could anyone comment on the recent suggestion that the chewing of pine pitch is associated with sarcoidosis?

DR. CUMMINGS: Does anyone know anything about the chewing of pine pitch and its relationship to sarcoidosis? I believe the cases reported, Dr. Chapman, came from your part of the world. You may wish to comment on that in your summary.

DR. WALLGREN: When we are speaking about pine pollen, we must know and say that they all belong to the same family, but they are not all the same. One thing that is important, in lower Sweden, where we have the heaviest foresting of pine trees, is that the incidence of sarcoidosis is not so high as in the areas just a little north. However, the pine trees in the north flower much less often, only every fifth or sixth year, but in the south, they grow faster and blossom more often. Thus, I think that the exposure to pine tree pollen must be less the farther north we go.

DR. CUMMINGS: Dr. Smith?

DR. SMITH: I will make this brief. I address this to Dr. James. I was intrigued by his young Irish girls who develop acute sarcoidosis with erythema nodosum about a year after they come to London. What happens to the girls who do not come to London, who stay in Ireland? Are they diagnosed as sarcoid in any of the centers in Ireland?

DR. JAMES: There is no series I can quote from Ireland of the various causes of erythema nodosum there. The most common cause of erythema nodosum in adults in Britain is undoubtedly sarcoidosis.

SUMMARY

JOHN S. CHAPMAN

A communication appeared in 1954 giving, as well as could be determined at that time, the worldwide distribution of sarcoidosis. It was not a very good survey because it was a long way from being complete. It was incomplete partly because professors of medicine and pathology at a good many medical schools did not bother to reply to letters asking them about sarcoidosis.

In any event, the summary of information obtained at that time from the medical schools which replied, from the good offices of the World Health Organization, and from Ministers of Health of several countries—Belgium and France particularly—led to the assumption that sarcoidosis has a tendency to appear in the temperate zones and to fade somewhat as one goes south, let us say, from northern Europe, or goes north from South Africa or from the southern part of South America. The absence of cases in the torrid zones may be explained very well on a number of different grounds, of course.

What did appear to be rather curious in the course of this study was the fact that at that time, so far as could be learned, the American Indians seemed to be largely untouched by the disease. In the interval since then, it has come to our attention that quite a number of cases have been reported. I know of four not reported, however, from the state of Washington. I know of the one mentioned by the Chairman, and I believe there has been one in a French-Canadian Indian, a half-breed. There has been a case in an Indian in North Carolina, in Dr. Harrell's original report, I believe. But the fact remains, so far as one can learn, that the American Indians living more or less according to their tribal customs, and in their original tribal location, still are not showing sarcoidosis.

It is true that many Indians live in that large blank spot shown on the Army, Navy, and Veterans Administration maps. Indians in that area appear to be spared from sarcoidosis, and the desert area seems to be free of it. At least, it has not been found in spite of many roentgenographic surveys.

The other point that seemed rather odd, as a result of those previous questionnaires, was that apparently the Chinese seem to be largely spared by sarcoidosis. This, again, may be a false impression. Part of the information came from Singapore, where a very large mass survey had been made about one year previously. Since then I have heard nothing to indicate that sarcoidosis is appearing in Singapore. The same applies for the University of California, where cases in Chinese had not been encountered. Whether this was because of the fact that the Chinese are seldom clinic patients, I do not know, but that is one possibility.

It does appear from the papers presented this afternoon that the reported cases remain mainly in the temperate zones; the torrid zone is still largely skipped, and the hot, arid area of the United States is still, to a great extent, passed over by sarcoidosis. I do not know about the Sahara, or about the inhabitants of the back country in Australia. Cases are reported from the major cities and universities of Australia.

The rarity of sarcoidosis in the Indian, and perhaps in the Chinese (if this can be verified) could very well lead to some important information. Whether these points can be verified further remains to be seen. Perhaps Dr. James in London can watch out for Chinese patients, because there are Chinese in London, I know. Perhaps some of the people in India and South Africa, and in the islands of the Pacific, can give us more information in time to come. So much then for what we can learn from the worldwide geographic distribution.

The general tenor of the papers this afternoon has been an extremely satisfactory one. Dr. McCuiston has undertaken the kind of study on a local basis, using various methods not hitherto applied, that I think can lead somewhere.

I should like particularly to compliment Dr. Comstock on his careful study of a few selected questions that may be pertinent, and I should add that I know a little about the problem of the eating of dirt. Among the patients with whom I deal, the habit is limited chiefly to young children and middle-aged Negro women with menorrhagia, and sometimes to Negro women during pregnancy. It is thought, and has been generally held among the medical people of our community, that this is a result of iron deficiency, and it is certainly true that the earth they prefer comes from an area in which there is very low-grade iron ore. Analysis of some of the soil revealed about 2 to 3 per cent iron.

The method of consumption is to roll the wet clay into pills, bake it, and swallow the pill intact. We have had in our hospital a few cases of complete filling of the large bowel with clay, and one gets the impression, upon seeing a flat film of the abdomen, that the patient is stuffed with clay.

The other cases that have been reported from various countries seem to me to follow a fairly

general pattern not unlike those already reported. The frequency of discovery in various areas apparently is, in a large measure, proportional to the enthusiasm and interest of the physicians in those areas.

There have been a few minor departures from the usual rule for sex and age predilection, but I think these may very well be explained on the basis of small numbers. In view of the very nice report Dr. Buck has just given, and to carry on a little further from Dr. Comstock's report, I am venturing to report largely from memory a rather carefully matched study that the Veterans Administration carried out. This report, as far as I know, is not yet in journals and perhaps never will be, since it was largely negative. Perhaps a session of this sort is the best place for negative results as well as positive ones.

At any rate, it was decided to prepare a very complete and extensive questionnaire which would deal with every place of residence since birth; every occupation followed; the type of bedding used in the home; certain construction features of the house, i. e., whether it had a dirt floor or any other kind of a floor; and the prevalence of insects, both those which attack man and those which apparently leave him alone. Habits of diet were covered by questions on the consumption of wild vegetables, wild fruits, wild berries, and game of all sorts, including such things as opossum, with which I was somewhat interested for a time. It included the consumption of dirt, the source of water supply at each residence, and many other similar details. The veterans with sarcoidosis were then matched against persons with other diseases, with respect to age, sex, and predominant place of residence. The results were negative. It became apparent that we had merely gone into the mode of life of a particular group of persons, some of whom had sarcoidosis and others who did not, but who otherwise resembled each other in all respects.

One or two other points seem to me to have emerged rather sharply from the Conference up to this time. The first of these is the rather curious point made in London two years ago that some Irish girls develop sarcoidosis within a year or two after they come to London, and usually in association with pregnancy. I believe that is correct.

The other interesting point, which emerged from the data presented by Dr. Gundelfinger and Dr. Cooch, is that individuals being separated from service after two years had come in with normal films and by discharge had abnormal films. Something like one and one-half or two years elapse both in the case of the Irish girls coming to London and the fellows going into the Army or Navy. Both experience a very marked change from their previous mode of life.

It could be that something at home restrains the development of the disease, or that the agent is freshly encountered under the new conditions. On this point it seems to me there is a possible toss-up.

Dr. James: What about the Puerto Ricans going to New York?

Dr. Siltzbach: The migrants get erythema nodosum either within a year or up to twenty-five years.

Dr. Chapman: In this regard it strikes me as of considerable interest that it was shown, for example, that the induced zirconium granuloma can appear in about six or eight weeks, just as the induced response to the Nickerson-Kveim test.

I have one other comment along an entirely different train of thought. Throughout this entire discussion when there has been opportunity to compare the white American with the Negro American, there have been one or two outstanding points: First, it appears that the Negro gets the disease younger in life, that he gets it more frequently, and that it often runs a more severe course. If one makes certain assumptions, which he probably should not do, he can say this is not unlike the way a new disease strikes an unprepared population.

That is one possibility. Against this point, and also against the significance of the two-year period, is the fact that the youngest patients have acquired the disease in what we regard as the endemic area. They have not changed their modes of life or their habitats, and they usually do not manifest sarcoidosis until five or six years of age. In addition, it is true that the Negro's mode of life in the endemic area may be such as to bring him into contact with large amounts of the agent or such as to depress his resistance to an agent otherwise only rarely pathogenic.

Dr. Cummings: We must now end this fascinating discussion. New information has been provided which should stimulate further more comprehensive epidemiologic study. One is left with the feeling that either many agents may incite the tissue response which we call sarcoidosis, or that we are still unaware of the single provoking agent responsible for this disease. I am more than ever convinced that the epidemiologic approach to sarcoidosis remains a most reasonable one. However, we still must ask the right questions under the proper circumstances to gain the insight we seek. Hopefully, I shall predict that someone will leave this Conference with the new idea which, when adequately tested, will solve our riddle.

PLENARY SESSION

ROBERT J. ANDERSON, *Moderator*

INTRODUCTION

DR. ANDERSON: The sponsors' hope for this Conference was that it would foster increased interest and investigative work in sarcoidosis and that it would facilitate the exchange of knowledge about it among scientists in many countries. To these ends, after the formal presentations and general discussions, each conferee was assigned to one of three discussion groups to review and summarize these aspects of the work: the laboratory, the clinical, and the epidemiologic. These groups summarized the significant facts in their areas and developed recommendations for future work by individual scientists and institutions. Their reports were presented to the full body of conferees and discussed, sometimes heatedly, before the final version as presented here was reached.

Noteworthy are the conclusions about the importance of certain physical and laboratory signs in arriving at the diagnosis, the usefulness and validity of the Kveim-Nickerson reaction, and the format of a clinical case-classification system. The classification system can be useful in analyzing and reporting data on any aspect of the problem and, moreover, will facilitate comparison.

It is the belief of participants in this Conference that further investigation can result in changing and improving some or all of these reports. This is the challenge to the reader: To probe, to test, to experiment, and to report in such a way that his observations and analyses will advance knowledge and find acceptance by his colleagues throughout the world.

REPORT OF THE MEDICAL GROUP

HAROLD L. ISRAEL, *Chairman*

The medical group considered the following topics:

I. Definition
II. Classification
III. Criteria for treatment
IV. Classification of results of follow-up studies
V. Clinical studies
VI. Research projects
VII. Future conference.

I. *Definition*. The group believed that a short descriptive paragraph would be more meaningful at this time than a definition. The descriptive paragraph is as follows:

> Sarcoidosis is a systemic granulomatous disease of undetermined etiology and pathogenesis. Mediastinal and peripheral lymph nodes, lungs, liver, spleen, skin, eyes, phalangeal bones, and parotid glands are most often involved, but other organs or tissues may be affected. The Kveim reaction is frequently positive, and tuberculin-type hypersensitivities are frequently depressed. Other important laboratory findings are hypercalciuria and increased serum globulins. The characteristic histologic appearance of epithelioid tubercles with little or no necrosis is not pathognomonic, and tuberculosis, fungal infections, beryllium disease, and local sarcoid reactions must be excluded. The diagnosis should be regarded as established for clinical purposes in patients who have consistent clinical features, together with biopsy evidence of epithelioid tubercles or a positive Kveim test.

II. *Classification*. The purpose of this outline is to encourage uniformity in the presentation of data. The following is recommended:

A. Anatomic distribution. Specify organs involved, including the presence or absence of erythema nodosum.
B. Known duration:
   1. Less than 2 years
   2. Two years or more.

C. Activity:
1. Active
2. Inactive
3. Undetermined.

D. Functional impairment:
1. Present
2. Absent.

E. Acceptability of clinical diagnosis. Groups I, II, and III, as defined in the following table, are acceptable but should be specified and analyzed separately. Group IV is acceptable for study under special circumstances, as in some epidemiologic investigations. Groups defined by all other possible combinations are unacceptable.

Group	Clinical Compatibility	Kveim Test	Biopsy Result
I	Positive	Positive	Positive
II A	Positive	Positive	Negative
B	Positive	Positive	Not done
III A	Positive	Negative	Positive
B	Positive	Not done	Positive
IV A	Positive	Negative	Negative
B	Positive	Negative	Not done
C	Positive	Not done	Negative
D	Positive	Not done	Not done

III. *Criteria for treatment.* Administration of corticosteroid hormones is the only method of drug treatment which is now known to be of some value. The following criteria are recommended for treatment with this drug:

A. Indications for administration:
1. Active ocular disease.
2. Progressive pulmonary involvement, as evidenced by increasing symptoms or roentgenographic changes, or impaired or deteriorating pulmonary function.
3. Persistent hypercalcemia or hypercalciuria.
4. Central nervous system involvement with significant functional impairment.
5. Disfiguring cutaneous lesions.
6. Myocardial sarcoidosis.

B. Dosage: The least dosage that will accomplish the desired clinical effect.

C. Duration of treatment: The minimal course of treatment is generally three months. In chronic cases, longer periods are frequently indicated.

D. Precautions: The usual precautions in long-term steroid therapy should be observed.

IV. *Classification of results of follow-up studies.* The following classification is recommended:

A. Improved with no residuals.
B. Improved with residuals.
C. Unchanged.
D. Worsened.
E. Death:
1. Due to sarcoidosis
2. Due to residuals of sarcoidosis
3. Unrelated to sarcoidosis.

V. *Clinical studies.* A clinical examination should include the following:

A. Roentgenogram of chest.
B. Roentgenograms of hands and feet; these are more useful in chronic cases.
C. Skin tests:
1. Tuberculin
2. Fungal skin tests in persons possibly exposed
3. Kveim test when validated test material is available.
D. Serum globulin; specify method used.
E. Serology for fungal disease.
F. Serum calcium.
G. Quantitative twenty-four-hour urine calcium when possible.
H. Sputum study for acid-fast bacilli and fungi.
I. Biopsy specimens stained with hematoxylin and eosin, including special stains for acid-fast bacilli and fungi. Cultures should be made.

VI. *Research projects.*

A. The proposed histopathology slide study should be carried out.

B. Controlled clinical studies to determine the efficacy of corticosteroids should be instituted, and a committee should be appointed to plan the details of such studies. These studies should be of two types:
1. In circumstances in which steroids are now regarded as indicated, comparative studies might be utilized to ascertain the relative value of short- and long-term therapy.
2. A controlled comparison of steroids versus placebo should be made in pa-

tients with subacute or chronic sarcoidosis not requiring therapy by present standards. The investigation would require long-term observation to determine whether or not steroid therapy influences the development of chronic or progressive disease.

C. The preparation, standardization, and distribution, on an international basis, of Kveim antigen is necessary.

VII. *Future conferences.* The group recommends that a conference be held in two or three years in another area to stimulate interest in the epidemiologic study of this disease and to evaluate the results of current and proposed research projects.

REPORT OF THE LABORATORY GROUP

DAVID T. SMITH, *Chairman*

I. The laboratory group recommends:

A. Circulation of a set of slides of human granulomas to a group of pathologists to be classified according to the degree of certainty in respect to sarcoidosis.

B. Circulation among pathologists for information and instruction of a second box of slides of Kveim biopsies labeled according to the degree of reaction.

II. There seems to be general agreement that the Kveim test is reliable and accurate when carefully prepared from potent material. Therefore, this group recommends:

A. The use of a Kveim antigen that is standardized for particle size and potency and prepared according to the general principles described by Dr. Merrill Chase in the paper presented to this Conference.

B. That a supply of such antigen be made available as a standard to investigators, both in this country and abroad.

III. Patients with erythema nodosum constitute a particularly valuable group to study from the standpoint of immunology. It is recommended that:

A. Serum be obtained from patients with erythema nodosum and stored in a suitable depository for future use.

B. Serum should also be obtained from patients with sarcoidosis who have acute febrile diseases without erythema nodosum and from those who undergo exacerbation.

C. The serum should be stored at approximately −20°C. without the addition of preservative.

IV. Dr. Sven Löfgren has succeeded in cultivating, in tissue culture, the cells from the sarcoid granuloma of man. The group recommends that tissue-culture studies from sarcoid lesions be expanded.

V. Since the possibility of an infectious etiology for sarcoidosis has not been eliminated, the group recommends that both animal inoculation and cultures be continued and expanded whenever this is possible.

VI. The group recommends that the technique of thin-section electron micrographs be employed in the study of sarcoid and other granulomas for the purpose of obtaining information in regard to the finer structure in cells constituting these reactions.

VII. The group recommends that continued studies of all phases of anergy caused by sarcoidosis be carried out not only on new patients and controls, but in a continuing manner throughout the various phases of the disease in the same patient. A variety of antigens, including those from the unclassified mycobacteria, should be employed in these studies.

REPORT OF THE EPIDEMIOLOGY GROUP

PHILIP E. SARTWELL, *Chairman*

The epidemiology group took as its task the consideration of proposals that would encourage and strengthen epidemiologic research designed to add to our knowledge of the etiology, occurrence, distribution, and natural history of sarcoidosis. In the light of these considerations, it is recommended:

I. That a series of systematic definitions and a classification of forms of sarcoidosis be developed and published in order to improve the comparability of data from various areas. The classification of tuberculosis developed by the National Tuberculosis Association, of rheumatic heart disease by the American Heart Association, and of coronary disease and hypertension by the World Health Organization are examples of what is needed for sarcoidosis. A framework should be provided that would permit the classification of cases in terms of activity of disease, anatomic sites of involvement, extent or severity and, possibly, stage of disease. It should also permit classification in terms of the degree of confidence with which the diagnosis of sarcoidosis can be held in the individual case, this depending upon clinical criteria, course of disease, and the results of laboratory tests. (Such a proposed classification was drawn up by the medical group and appears in that report.)

II. That studies be undertaken, preferably on an international basis, of the consistency and repeatability of two elements which are currently heavily relied upon in the diagnosis of sarcoidosis:

A. The histopathologic findings in tissues removed at biopsy or necropsy.

B. The Kveim reaction.

It is suggested that the Committee on Sarcoidosis of the National Academy of Sciences-National Research Council explore the feasibility of doing such studies.

III. That epidemiologic studies done to the present time show the importance, in any comparison of the frequency of sarcoidosis in different groups or areas, of giving careful attention to the following factors:

A. The identification of the population in which the cases are found.

B. The methods of case finding and the intensity with which they are pursued, and the methods of sampling, if used.

C. The diagnostic criteria for acceptance of a case.

D. Whether the case frequencies obtained should be regarded as measurements of prevalence or incidence.

E. Classifying both the cases and the population in which they were found according to relevant characteristics, in order to permit estimation of rates specific for these characteristics. Examples of such characteristics are race, age, sex, and urban or rural residence.

IV. That intensive epidemiologic studies of the retrospective case-control variety, designed to test specific hypotheses, be further undertaken. The study reported to this Conference by Comstock, Keltz, and Sencer is an example of such a study.

V. That efforts be made to obtain from various countries mortality rates from sarcoidosis, similar to those presented during the Conference by Moriyama, as well as morbidity statistics.

VI. That additional workers be stimulated to undertake studies of the epidemiology of sarcoidosis, and that they be provided with training and assistance.

Discussion

Dr. Anderson: We now have the reports of the three groups before us. Before we take action on these reports, is there any discussion with regard to the specific recommendations, or to anything that seems unclear or in conflict between the various reports?

Dr. Horwitz: There was one point made by the clinical group that I did not quite understand. In the clinical definition of sarcoidosis, you excluded patients with a local sarcoid reaction. I do not understand what that means. Many of our patients in the Institute have very slight skin lesions. Should these lesions not be regarded as sarcoidosis?

Dr. Israel: I think the clinical group took the position that you must demonstrate systemic involvement, not just a single isolated lesion, in order to classify the disease as sarcoidosis.

DR. CHAPMAN: What you are trying to exclude are the local lesions that occur from tattoos, scars, or something of that nature, which are unrelated to systemic disease.

DR. ISRAEL: Or the local reaction secondary to a carcinoma. These are not regarded as sarcoidosis and should be excluded.

DR. NELSON: Dr. Horwitz's difficulty is that he has seen a number of patients who have miliary or micropapular lesions involving only the skin, without any evidence of hilar adenopathy or blood chemical changes. He considers these, by your definition, to be local sarcoids, and we do not.

DR. HORWITZ: For instance, if it is only a spot on the nose, it is not sarcoidosis. Let us suppose you have a patient who previously was tuberculin positive, becomes tuberculin negative, and gets such a skin lesion. Is this a systemic reaction or is it only a local reaction?

DR. ANDERSON: Dr. Smith said to do the Kveim test on such an individual.

DR. MICHAEL: The objection to local sarcoid, as I understand it, does not concern the patient with a skin lesion who may later develop pulmonary changes. Rather, it is the isolated person who has, for example, a peptic ulcer, in whom sarcoid tissue is found and called sarcoidosis, or in whom the sarcoid reaction in a carcinomatous lymph node is called "sarcoidosis." I think that is the group we want to exclude. Am I right?

DR. SHELLEY: I think we have to spell this out with regard to the skin. After all, sarcoidosis was first recognized in the skin. As Dr. Horwitz pointed out, we do have a unique opportunity to see sarcoid lesions in the skin when they may not be evident in the lungs or elsewhere. It would be regrettable if we framed a definition which left out widespread cutaneous disease, such as Dr. Van Lingen reported. All forty of his cases might well have been eliminated from consideration, epidemiologic and otherwise, if we phrased the definition with such exclusions.

We deal with the same problem frequently in dermatology. We have localized scleroderma, which we call morphea, and no dermatologist can find evidence of it elsewhere in the body. Yet I am sure it is the same disease that we see with systemic sclerosis. Chronic discoid versus systemic lupus erythematosus is another example.

Thus, I think the skin lesion has to stand as an exception. If the physician is satisfied that it is a foreign-body granuloma, a zirconium granuloma, or a granuloma related to some disease like carcinoma, for example, he should eliminate it; it should not be considered sarcoidosis. I would like to hear what Dr. James has to say about skin lesions in patients who show no other signs.

DR. JAMES: I think we are talking about a very small segment of cases. Do not let that extremely small segment bog down an important international description or classification. There must be an occasional exception, but I think if you go down the middle of the road and give the world a broad description, that is as much as you can do today.

DR. CHAPMAN: Mr. Chairman, if the patients Dr. Horwitz is citing have a diminution in tuberculin-type hypersensitivity or react to Kveim antigen, I am not sure but that they have systemic disease, regardless of the fact that the lesion may be a very small or limited one. Some real change has taken place, even though the formation of noncaseating tubercle may be limited to one or two places on the nose.

DR. JAMES: This was emphasized in Dr. Van Lingen's communication, because he said a good dermatologist saw a few cases, and vice versa. We are not talking about that here, because these people know sarcoidosis. However, this description you are giving is going to go out to North Africa, where a patient may have a local area of leprosy on a finger, and you will want to guide them. It is therefore important not to allow any single pimple on the skin to escape from your exclusion clauses.

DR. ANDERSON: I am going to ask the Chairman of this working group to consider this matter and see whether he, with consultation of others who are present, can meet this problem satisfactorily, not only in the light of the definition, but in the light of the clinical classification. There were no other exceptions to the report of Dr. Israel and his group, so I regard the report as being acceptable and approved by the Conference.

I would like to turn now to Dr. Sartwell's report for the epidemiology group. We have his recommendations as to the important things that are to be considered in the classification of the forms of the disease, sarcoidosis. Did anybody find exception or think of additions that might be made to those listings? Would the chairman give them briefly, please.

DR. SARTWELL: Of course, we are pleased to find that one of the things we suggested be done, i.e., a classification of cases, has already been done by the clinical group. We also recommended that such a classification be published or made widely available.

The recommendation for studies on the consistency and repeatability of histopathologic findings and the Kveim reaction came from all three groups. There was remarkable unanimity of opinion, it seems to me, on a number of recommendations, such as the comparison of the frequency of sarcoidosis in different areas, intensive epidemiologic study related to a specific hypothesis, an attempt to obtain national data from a

number of countries on mortality, and a hope that additional work and workers in this field might be stimulated.

DR. ANDERSON: Are there additions or exceptions to this report? I might say that the recommendation on histopathology, both in biopsy material and Kveim material, did come from all three groups. So, it might stand out as universal. In fact, all of these things are universal actions of the Conference.

DR. LONG: I would like to say that the report of this group appears to be restricted to recommendations. Is that not true?

DR. SARTWELL: Yes.

DR. LONG: The report from the clinical group was somewhat more informational. I feel that we are in need of agreement on certain of the epidemiologic features of sarcoidosis. It is difficult to reach decisions on matters in which there is no agreement. I had hoped that there would be some consideration of what we do know, or at least, what we agree upon with respect, particularly, to the present distribution of the disease.

DR. SARTWELL: There are statements that can be made with respect to a few areas in which studies have been done, but whether these statements have relevance to other areas is a little dubious. For example, we can say that the frequency in Negroes in the United States is at least several times higher than in whites; I do not know of any exceptions to that. We could also say that it appears to be highest in frequency in the third and fourth decades of life. I wonder, Dr. Long, if such statements will not be found in the individual reports. At the present time I think the data are too meager and conflicting for firm general statements with respect to other epidemiologic characteristics, such as geographic distribution.

DR. LEBACQ: Up to now we have had many cases clinically diagnosed as sarcoidosis which have not been entered in our statistics because we have had no biopsy available and our Kveim extract is not good. For the time being, we find 25 to 30 per cent to be Kveim positive. We learned at this Conference how to prepare good Kveim extract. However, for this year and probably for next year, we will not have good Kveim extract. What will we do?

DR. JAMES: Liver biopsy.

DR. LEBACQ: Yes, we do a liver biopsy each time. However, in 65 per cent of the patients the result is positive, but there are 35 per cent in whom nothing can be found. I would like to know how I am to send the enlarged spleen that I find to Dr. Chase.

DR. CHASE: Send it to me frozen.

DR. ANDERSON: I think that the report that Dr. Lebacq seeks is covered in the classification scheme. As Dr. Nelson points out, you can identify your patients as being in either Group IV or one of the other groups, according to the work-up that has been done.

The report from the epidemiology group is approved, and we will proceed to Dr. Chapman's report for the laboratory group.

DR. CHAPMAN: This report dealt with some matters that are already under way, or partially under way. The first of these was that Dr. Johnson of the Armed Forces Institute of Pathology, as you know, has agreed to prepare a set of slides to determine how accurate pathologists think their diagnosis of sarcoidosis may be. He now has five boxes containing twenty slides. The idea is to get twenty-five slides and send these sets to a number of pathologists to see how close histologic agreement is. The second matter discussed and recommended was the preparation of slides showing varying degrees of the Kveim response for circulation to pathologists. In this case, examination would not be blind, but would be marked 1, 2, 3, or 4, according to the certainty of the response. These slides are primarily for the instruction of pathologists. Since Dr. Johnson has agreed to this, it was included as our first recommendation.

DR. SILTZBACH: There is a problem to which I believe Dr. Uehlinger might best address himself. The purpose of the first recommendation, as I understand it, is to send slides of many granulomas and to ask the participants to indicate those that might be compatible with sarcoidosis. They will not be able to make the diagnosis of sarcoidosis on the basis of tissue section alone. I think that must be made clear.

DR. CHAPMAN: Yes. Possibly some of these will not have giant cells in them or anything of that sort. The object is to find out what a pathologist in a particular hospital will label as sarcoidosis.

DR. SILTZBACH: The pathologist will, I am afraid, have to hedge on all the slides from the standpoint of making a definite diagnosis. He will say "it is consistent with."

DR. CHAPMAN: Yes. The next recommendation was that a Kveim antigen be standardized for particle size, potency, et cetera, and the further recommendation that a supply of such antigen be made available to investigators both in this country and abroad. All we can do at the moment is to make recommendations. We hope that some mode of action will develop from this working group's recommendations, as well as from those that have come from the other groups.

The third point was more in the nature of a comment which arose from the interest of the group in immunologic responses of patients with sarcoidosis. It seemed to the group that the patient with erythema nodosum is a rather exceptional

individual, and might very well show some rather interesting immunologic and serologic responses. Thus, it might be wise to secure serum from such patients, even though at present there might be no specific test to be used on such specimens. It is suggested that such serum be saved until the time when something better than we have now will be available. This is essentially the sense of this recommendation.

I might add that Dr. Ralph Vogel and I are very anxious to obtain serum. We would be glad to receive any that anyone would want to send us from any corner of the country or of the world.

It was also thought that, in addition to the patients with erythema nodosum, it might be particularly interesting to study those rare individuals who happen to have sarcoidosis without erythema nodosum but who have rather consistently elevated temperatures, and those who show rather sudden progression of disease, involvement of a new system, or something of this nature. These cases could very well prove to be highly interesting from an immunologic standpoint.

DR. ANDERSON: You will want case information material along with the serum, then?

DR. CHAPMAN: It will be desirable, of course, to know from what particular type of patient the serum came.

DR. ANDERSON: That point should be specified in your recommendations.

DR. CHAPMAN: Recommendation number IV was that tissue-culture studies shall be continued. We do not know whether this type of study will lead anywhere, but there is certainly every reason to continue efforts in this direction.

DR. ANDERSON: Does anyone wish to elaborate on that or to comment on the tissue-culture study continuity recommendation?

DR. SMITH: We were trying to plan for the future with reference to this point, and we could visualize the possibility that someone would be able to get nicely spread-out cells in tissue culture. Then perhaps one could tag an antibody with fluorescein, even though they did not know the name of the antibody. Perhaps some particular granules inside the monocytes could be fluorized, and we would be just a step further toward identification.

DR. BELNTON: I would like to speak on a previous point, with reference to the Kveim antigen, if I am not out of order. There has been a giant step forward during this Conference in the reporting of antigen which is fairly homogeneous, and in that results obtained from its use in the skin are reproducible. It is also reported that this can be used just as a standard, and antigens made from other sources can be compared with it.

I know from talking with other members of the Conference that many of us are interested in having our antigen standardized so that we can all be working with the same material. The Kveim test occupies an important part now in our definition and classification of the disease. I wonder if the Chairman has any ideas of how members of the Conference or other individuals could concern themselves with the establishment of a laboratory which would be equipped to accept materials from all parts of the world and to prepare antigen from this material. Will those most intimately concerned express a willingness to standardize antigen? This information would give us something. Dr. Smith spoke to this point at a previous session when he talked about Old Tuberculin and its standardization.

DR. ANDERSON: Dr. Chapman said he did not believe this was quite the place to take up the mechanisms through which one might actually produce a standard Kveim antigen and make it available to workers throughout the world. I think I agree with him on this point. There are a number of different ways that this can be accomplished, possibly through Dr. Chase or a commercial firm. I do not believe that we could settle at this time, in this place, on the one possibility that really would be the source of a supply of standard antigen.

DR. SONES: Would it not be correct, however, for this Conference to emphasize the urgency of this matter? If this is delayed, it might be for a year or longer, and our classification and criteria, in some instances, would depend on an acceptable Kveim antigen.

DR. CHASE: While it may constitute an interruption to your general train of thought, I would like to make one comment that may clarify the issue. To prepare testing suspension is one matter; it is quite another to receive some new spleen to be prepared, evaluated, and returned for use with a recommended dose level. Such effort demands a clinic with available sarcoid patients, and there are few such clinics. This requires an established clinic to give us the value, not only for normal individuals who must be sought, but also for tuberculin-negative and tuberculin-positive patients. The evaluation may be a long, slow procedure. If we were to possess three properly evaluated spleens, the preparation of adequate supplies of testing suspension could be made in any carefully conducted laboratory with bacteriologic "know-how."

Therefore, it seems to me, at present, that no more than three splenic sources should be contemplated because you will be dependent upon the generosity and the willingness of a clinic staff to make tests on a series of patients with different dilutions and different routine injections. Of

course, patients must be willing to receive multiple tests. I think that we have to aim at a move that is small at the moment, but with splenic tissue large enough in bulk to give us repeated batches.

DR. SILTZBACH: May I briefly amplify that point? We have had some experience with calibrating four Kveim antigens for the Veterans Administration, and it is a complicated matter. I would suggest that rather than attempt to do this in any one place, at least two institutions should participate in a coordinated program of calibration and standardization of Kevim suspensions. I think it would be very difficult to do any great amount of work in any one place. A steady flow of patients is but one of the requirements.

DR. ANDERSON: We are really talking now about the details of production. First of all, with regard to obtaining material, its production, and standardization, these would have to be taken up by a special group. Let us now consider recommendation number V.

DR. CHAPMAN: The working group thought that at this time there is insufficient evidence to eliminate the possibility that sarcoidosis is infectious in nature. The group, therefore, recommends that there be continuing experimentation with cultures, animal inoculations, et cetera, according to an individual's desires, abilities, and the means at his disposal.

Recommendation number VI concerned the desire to employ thin-section electron microscopy in the hope of learning something more about sarcoidosis or perhaps about granulomas in general. This is merely a recommendation and depends, of course, upon the availability of electron microscopes. Last, the group recommends that continued studies of all phases of anergy caused by sarcoidosis be carried out not only on new patients but in a continuing manner in the same patients. In other words, we do not believe that patients who have been tested once and found to be anergic can then be forgotten; they should have repeated tests. Furthermore, in these tests a number of antigens might profitably be employed.

DR. ANDERSON: What is your wish with regard to this report of the laboratory group? Adoption has been moved and seconded. It is passed and adopted.

We have then the sum and substance of the Conference and its findings. The work is not finished; this is but a progression in the elucidation of sarcoidosis. Dr. Esmond Long will now summarize the Conference.

SUMMARY OF CONFERENCE

ESMOND R. LONG

On the whole, Mr. Chairman, I feel that my task is superfluous. I have attended a good many international meetings, and I do not think that I ever attended one where the conference had the subject matter of the deliberations as well in hand, when they got around to the point of writing recommendations, as has been the case this time.

Usually the groups that come together are more or less confused and have forgotten a good deal that has already been said. They have difficulty in reaching decisions because of that fact. Then they leave much more to the working committees or to the organizing committee than has been the case here. I may say that I was asked by Dr. Chapman whether these recommendations should be considered as charges upon the organizing committee. I believe that if they are turned over to the committee in clear fashion, nature will take its course and a proper action will become apparent.

In view of the lateness of the hour, and also because much of what I had in mind to tell you would be boring now that you have organized the material so well, I shall condense what I intended to present and begin by making some comparisons with previous meetings.

It is customary at this hour, as Dr. Sartwell did, to disclaim being an expert in the field, and I cheerfully join the same group as Dr. Sartwell. I am no expert in the field, but because of a long association with the National Research Council, I have had some responsibilities, fortunately growing smaller, in these meetings. You know that the first meeting was in 1948, and the second, of the American group, took place in 1956.

I recall that on comparing our work in 1956 with what had been done in 1948 we left with a feeling of self-satisfaction in the belief that we had sharpened our understanding of sarcoidosis. Somewhat in contrast to our complacency on that occasion, my impression this time is that we have sharpened our ignorance on the subject. But actually the two points of view are more or less the same.

We had a cloudy picture of sarcoidosis when we began meeting to discuss the subject twelve years ago. We have a much clearer picture today. We have tended in our debates to bring out those matters on which we need much more information. I think the recommendations are quite clear as to what the group should do. One of the most important recommendations for the future, it seems to me—and I do not recall if it was expressed in so many words—is continuation of international gatherings. It seems to me that the variety of experience from all over the world, and some differences that have been exposed in looking at each others' experiences, make it mandatory to consider further work on this problem through international pooling of effort.

When I began to plan my discussion, I wrote down that I have seen very little or no tendency this time to rewrite the definition of sarcoidosis. I now have had to change what I wrote, however, because the definition actually was rewritten, and I think very well, by the clinical group.

Worth noting, in my opinion, was the fact that, in spite of previous feelings of dissatisfaction with our definitions of the disease, at least one of the speakers in the first session said that, regardless of the definition, it appeared that we had in our minds somewhere, subconsciously or consciously, a good working definition, because we were all quite certain, as far apart as we were in our origins, that we were talking about the same thing. As it turned out, however, we have gone ahead and we have a new definition, which I think puts us somewhat forward.

I shall now proceed to run down rather briefly some of the matters that seem to me to be highlights.

As was perfectly proper, working groups were established to consider the laboratory diagnostic criteria, the clinical aspects, and the epidemiology of the disease, and they came back with certain recommendations for future work. What I have to say might not agree with what all of you have to say. Anyone is somewhat subjective in his analysis of what has been said. While I am trying to be objective, I am sure that there is a subjective element in what I consider the high spots.

As to the laboratory aspects, I thought we had a very fine delineation of the histologic characteristics of sarcoidosis. It was presented to us quite clearly in Dr. Hardy's opening talk that there are numerous other states which, at least locally, have almost identical histologic characteristics. But we came away from that presentation with a pretty good picture of what the disease is like, anatomically.

I may say that when I stepped into the epidemiologic meeting for a few moments this morning, I heard one or two bits of discussion that made me feel that perhaps the epidemiologists were not entirely satisfied with the criteria for histologic recognition on which agreement was

reached. But I find I am wrong and that the clinicians and the epidemiologists are willing to accept, for epidemiologic reporting, such a phrase as "consistent with the diagnosis of sarcoidosis."

In the past, I found the epidemiologists to be in a bit of a hurry, wishing the pathologists would make up their minds and not use such statements. I still think they might draw the line a little more strictly on the less definitive phrase "not inconsistent with the diagnosis of sarcoidosis."

I thought I detected an increasing respect for the chest roentgenogram, and all will agree that throughout the Conference there was a new emphasis on the immunologic value of the Kveim test. As I look through the old records, it seems to me that this is a clear departure from our previous considerations. The Kveim test has been discussed ever since we began having the meetings. The test is some twenty years old, and our conferences are only twelve years old. In the previous conferences it was washed out rather rapidly. Now a rather high degree of value is claimed for the test, provided two criteria are satisfied: that the material comes from a suitable source, and that splenic material is worked up by a well defined and not hasty method. Dr. Chase and his group are well prepared to fulfill these requirements.

It was stated over and over again that three-quarters of the patients who are diagnosed as having sarcoidosis on the basis of various established criteria react to the Kveim test. That left me thinking about the other quarter. I know that the rest of you who watch television and hear that three doctors out of four subscribe to treatment with a certain drug always wonder what is wrong with that other doctor and why he never seems to join the fold. But perhaps it is equally important that there appear to be very few false reactions, very few reactions when no other evidence of what we call sarcoidosis is present. The missing quarter may only be of different character. It may be only a matter of degree of sensitivity to the test, or there may be genuine difference of another sort on a three-to-one basis. That is one of the problems we are to solve.

As to laboratory analysis, and again I am thinking back to the previous meetings, there was renewed appreciation of the evidence on disordered calcium metabolism. But the workers in that field have now gone into the question more thoroughly and tried to pinpoint the trouble. As the chief speaker on that subject said, the phenomenon with which we appear to be dealing is some sort of hypersensitivity to vitamin D or, as another worker expressed it, sarcoidosis involves an indigenous intoxication with vitamin D.

I remember in the past a great deal of discussion about hyperglobulinemia. That seems to be accepted today, and not very much discussion took place. It was included as significant within the clinical description of the disease.

All of us were much interested in the symposium concerned with granulomatous responses, whether they were to be called sarcoidosis or sarcoid reactions. It is remarkable that such a degree of granulomatous reaction can be set up through some type of systemic allergic response. I was particularly interested, myself, in the renal involvement shown. Also, there was more emphasis on zirconium than I, for one, had ever heard before. I thought those were extremely important results. There was emphasis on the fact that the degree of colloidal dispersion of material is intimately concerned with the capacity of that material to set up the granulomatous reaction.

There was much emphasis on the value of tissue-culture studies. We have not yet attained the understanding we would like to have, but the discussion opened up a good many leads, particularly with regard to the nature of those inclusion bodies, described so well, that take the periodic acid-Schiff stain.

On the whole, the diagnosis of the disease still appears to be fraught with many difficulties and pitfalls. There was some disagreement on the several characteristics I have mentioned, but I was impressed at all times with the concord in feeling that we are dealing with the same thing and, apparently, dealing with an entity.

As to the clinical aspects of the disease, we have had so much discussion of that this afternoon that it is not necessary for me to run over many of the notes I have set down. I might make one point, however, viz., that I have a new concept of the gravity of the disease as a result of the considerations set forth. Many of us, particularly those who have seen roentgenograms diagnosed in mass surveys and have watched the disease clear up, have been inclined to think of it as a pretty mild affair. Enough was brought out today to indicate that the process is one of considerable gravity. A number of us, I may say, attended a press conference this morning, at which Dr. Cummings was asked to make a quick estimate of the frequency of cases that might be considered grave. There was agreement within the group with his estimate that a fourth or a fifth of the sarcoid patients have sufficient complications so that the disease is more than a transient affair of no particular importance. To put it briefly, sarcoidosis is a graver disease than many of us have been accustomed to think in the past. Those of you who are specialists in the subject have always seen severe eye and kidney and other progressive lesions, and probably never did have the concept of the disease as a benign affair.

One valuable feature in the discussions, it seems to me, was the emphasis laid upon the prognostic value of certain types of lesions. You will all recall that patients who had significant involvement of the skin, eyes, bones, and kidneys were recognized to have a bad prognosis, or at least to be difficult to treat. In some of those patients there was rather advanced involvement of the lungs; this, however, showed a remarkable tendency to clear up and was considered not so grave. It seems remarkable that this was the case, in view of the fact that the lungs, with their great blood supply, should be the best source in the body for dissemination of the agent of the disease, if there is such a thing as a single agent.

The classification considered this afternoon on transient acute and chronic persistent forms of sarcoidosis was certainly a step forward in our attempt to separate the disease into compartments so that we can discuss it more clearly.

The attention to associated conditions, such as erythema nodosum and arthralgia, gave us new points of view. I do not believe there was any clear agreement, though, as to whether some of those associated conditions are to be looked upon as essential parts of the picture, i.e., always present to some slight extent, or as incidental findings present in some regions and not in others. I think I detect the feeling that pulmonary involvement in some degree, not necessarily advanced, is always a part of the picture. At any rate, it was the consensus of the speakers that much depends on how carefully you look for different manifestations.

By and large, I think most clinicians make a diagnosis of sarcoidosis without necessarily including the eyes in the picture. Those who reported from the ophthalmologic point of view, however, made it clear that if the eyes are examined carefully enough, in all their parts, some degree of eye involvement will almost certainly be found in any significant case of sarcoidosis. The terminal result of the eye involvement, glaucoma, was stressed as of great importance for our attention.

As to treatment, that has been discussed so much here today that I hardly need to add anything more than a few impressions of my own. There is a rather general reliance on the adrenal corticosteroids. I should note, however, that we had an exciting paper about chloroquine. I do not believe it was stressed among the methods of treatment to which attention was called in the clinical summary. So I will simply note that here is a drug that was introduced originally for malaria but was later recognized as of more or less value in other diseases, and for that reason was tried out in this curious disease. In the series reported, it seemed to have considerable value.

A remarkable fact in the figures given on treatment with corticosteroids was that in any large series of patients the outcome appeared to be approximately the same, on the average, in those treated and those not treated. But it was soon evident to all of us that there was a good reason for this phenomenon that could be found in the selection of the cases for treatment. There is a certain amount of hazard in the use of corticosteroids, and for that reason the drugs are usually withheld in treating the mild cases, which may soon clear up anyway. Therefore, the patients with originally bad prognoses are those who receive the treatment. For that reason, no clear-cut favorable effect of these drugs has been noted.

I have by no means exhausted the clinical subject, but will pass on rather quickly to the last of the three categories, namely, epidemiology. That is an extremely difficult one to summarize. First of all, it seems to me that the advantages of internationally pooled effort have never been more clearly demonstrated than in our discussions today. In fact, if we are going to consider the epidemiology of the disease, we cannot limit our perspective to any single country or restricted locality. The indications were that it was definitely worldwide in its occurrence, and that, biologically, it had essentially the same characteristics wherever it occurred.

After you have said that, you enter what seems to me to be a realm of considerable confusion. The collective figures reported to us from various places in the United States and other countries differed a great deal, apparently not because of fundamental differences in the disease in different localities, but primarily because of the character of the selection exercised in assembling material for study.

The cases were selected rather largely from groups subject to diversity of material and, therefore, diversity of result. Many figures come from clinics or hospitals, including chest, skin, eye, and orthopedic clinics. One of the most important studies of all, of course, because of the volume and the homogeneity of material, was in the hospitals of the Veterans Administration in the United States.

We saw figures from certain selected population groups, which were valuable as far as they went. The studies of military forces formed one of the best examples and provided the clearest results. But it must be remembered that these groups did not include women, children, or old people. Nor were they exactly representative of the populations of the different countries, racially, economically, and so on.

Finally, some of those who reported their epidemiologic experience simply took whatever cases they had on hand and analyzed the accumulation.

In spite of all that, it seems to me that certain points stood out. One of these was that there is an excessive prevalence of the disease in Negroes, at least in the United States. That was not confirmed for other places. Ten to one was the figure that was often quoted. Also, there was a certain geographic distribution within this country. However, that distribution seems to be expanding. So the figures made some feel that if we keep the study up long enough and in enough other places we may find that the disease is not as concentrated in certain localities as we now think. When you mention a geographic locality, obviously you are using a term including many factors besides location alone. There was a slight preponderance in the rural areas, and again the fact was recognized that many factors might be concerned. The majority of speakers, it seemed to me, reported some excess of sarcoidosis in Negro females. The disease is recognized as relatively rare in childhood, but everybody who reported had seen some cases in children.

By and large, the major ecologic considerations were left unsolved. Quite properly, a large amount of consideration was given to the degree of correlation with pine growth and pollen dissemination. This consideration, it seems to me, was especially important in light of the fact that we had at least one laboratory study indicating the capacity of the pollen to stimulate granuloma formation and, at the same time, to sensitize to further granuloma formation.

On the whole, a correlation with pine pollen has not been solidly established, in spite of a number of suggestive leads. It seemed to me, and I think to many of you, that the relation of pine pollen to the disease was left equivocal. A few areas are left to be explored that may have certain key characteristics for further study.

Much attention was devoted to the prevalence and incidence of the disease in the successive reports. Some of us tried to come up with an average figure. Figures were given of a mortality of 200 a year for the United States, or approximately 1/10,000 of all deaths. I hope those two estimates agree, although I am not sure they do. By and large, the prevalence reported seemed to be between one per 10,000 and a maximum of 10—I think in New York—per 10,000. But the point was made, and there seemed to be general nodding of heads around the room, that in all probability the disease is much more common than is ordinarily suspected.

I tried to write down a bit about the disease as it was reported to us in the different countries. However, the material is so diverse that it is really fruitless to draw any conclusions from my notes. There were a few points that I might call to your attention. In Scandinavia sarcoidosis appears to be a "people's disease," in which no particular social factor such as poverty or slums is concerned, and the illness seems to permeate the various levels of the population. I believe somewhat similar considerations apply to Scotland and England. Most of the cases in those countries were described as mild, but there were exceptions. The word from Belgium, as I recall, was that study there was only getting under way, so that reliable figures could not yet be given. Switzerland reported a prevalence more or less in proportion to the density of the population. Japan gave us the very interesting fact that the figures were based almost entirely on mass surveys, and were highest by far in those parts of the country where there were good medical schools and, presumably, therefore, good diagnoses.

In South America, more cases were found in Uruguay than any place else. But I know that in no other place in the whole continent are roentgenographic surveys carried out on such an extensive scale as in Uruguay and, particularly, Montevideo. That fact seems to account for the relatively high percentage of cases noted there.

All of us were interested in the report from South Africa. Correct me if I am wrong, but we had the feeling that two months ago South Africa was free from cases of sarcoidosis or, at least, cases were not known in any significant number. But we were told by the speaker that he was delighted to have the invitation, that it came only two months before he had to appear here, that he had to work pretty fast, and that the harder he worked the more cases turned up. We were left with the impression that, in time, not a few cases might be discovered.

Fortunately, you took your actions in the light of greater knowledge than I have given you in this summary. All I have done is give you a kind of objective instead of subjective roundup. I would say in conclusion, and this is subjective, that you certainly worked well together. There appeared to be, in the first place, a sense of comradeship in the job in which we are engaged, and I am sure I am right in saying that there was a real sense of satisfaction that we have had a chance to get together here and thrash out the problems in the way that we have.

There was universal appreciation of the value of the preparations made by the Committee on Sarcoidosis of the National Research Council, of which Dr. Cummings is Chairman, and I am sure that even those of you who are not familiar with the mechanics of staging the Conference know that we are all greatly indebted to our various hosts on this occasion.